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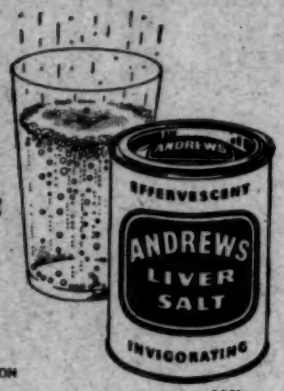

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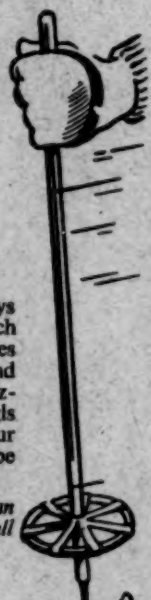

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 22 1955

MITRAL VALVOTOMY: A FOLLOW-UP OF 45 PATIENTS FOR THREE YEARS AND OVER

BY

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AND

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(From the Cardiac Department and the Thoracic Surgical Unit, Guy's Hospital)

Mitral valvotomy is now an accepted treatment for stenosis of the mitral valve and is practised throughout the world by thoracic surgeons, using the same approach and established technique. As mitral stenosis is a common disease, the operation is a frequent and routine procedure in all large centres, and probably 100 valvotomies are undertaken every week in Great Britain alone. The stimulus of this practical treatment has produced many clinical observations and research investigations of varying approach which have added greatly to knowledge of the local and general effects of mitral disease. Mitral valvotomy has shown that the dominant factor in the widespread and differing manifestations of the disease we have long known as mitral stenosis is, in fact, the stenosis of the mitral valve, although the importance of this factor varies in the individual sufferer.

Detailed observations of the varying clinical picture correlated with the signs and measurements have been checked by observations and measurements of the valve in life and action—a most important advance which is well exemplified by Paul Wood (1954) in his Strickland Goodall Lecture—and this has to some extent simplified and clarified what was before confusing and obscure. It is agreed that a successful operation, which relieves a critical degree of stenosis, relieves or banishes the patient's disability and makes the dynamics of the circulation measurably more normal. How lasting this effect is, how it changes the course or natural history of the disease, how it alters the prognosis of the individual patient, have yet to be learnt. The necessary interval of time to follow enough patients who have had a mitral valvotomy is still much too short, but despite these recognized shortcomings we have some evidence to make some preliminary observations.

Scope and Material of the Present Follow-up

Our first patient was treated by mitral valvotomy on September 16, 1948. In June, 1950, we reported six successful operations and two deaths (Baker, Brock, and Campbell, 1950), and stated that "the results in this small series are good enough to show that valvotomy is a thoroughly practical procedure and can now be justifiably recommended in suitable cases." By January, 1952, Brock had operated on 100 patients at Guy's and Brompton Hospitals, and in May, 1952, with Paul Wood, we reported these, with a follow up of the first 50 patients (Baker, Brock, Campbell, and Wood, 1952). At the end of 1954 we had 27 patients who were in their fourth year after operation at Guy's, 14 in their fifth year, 3 in their sixth year, and our first patient was in her seventh year: these 45 are reviewed here. Three patients were excluded from the follow-up as they lived abroad and we have insufficient information about them, and we are confident that we have had close and personal contact with the progress and present state of the 45 we are considering. In a minority whose distance from Guy's has made a journey difficult we have had information both from them and from their doctors or physicians, with *x*-ray and electrocardiographic evidence, and have insisted on seeing them personally only if the evidence was in any way equivocal. All 45 patients had a cardiac catheterization before operation; 29 had this repeated after operation, 5 of them more than once. The short time since operation and the small number of patients limit the significance of the follow-up at this stage, but we think that certain observations can and should be made now. Though a much longer period is needed and will no doubt modify our present conclusions, we are also convinced that the number of patients followed should be no larger than can be individually and thoroughly known as persons as well as patients.

In assessing the clinical state of patients both before and after operation we have used the grades of disability that we defined in detail in 1952 (Baker *et al.*, 1952); in the simplest terms these can be summarized as 0, no disability; 1, slight disability; 2, moderate disability; 3, gross disability; and 4, total incapacity.

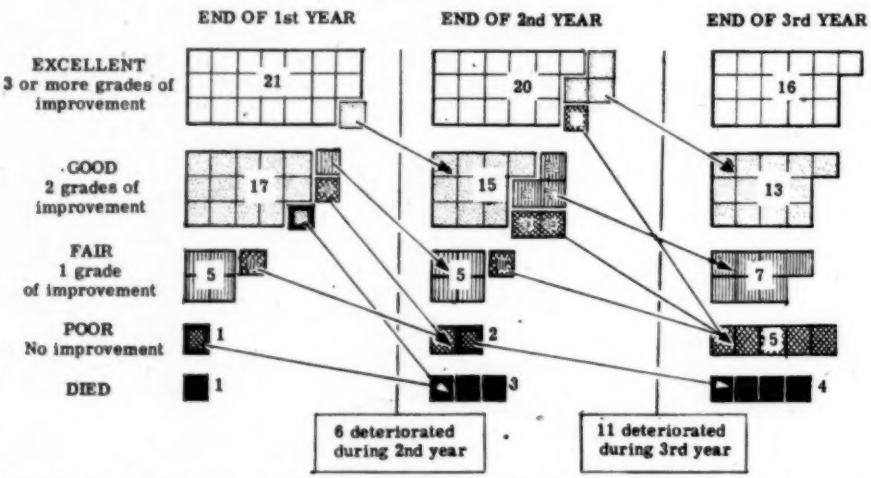
The pre-operative state of the 45 patients was: 20 in grade 4, or total incapacity; 24 in grade 3, or gross disability; and 1 patient who was graded before operation as 3, has, with subsequent knowledge of her, been reassessed as 2, or moderate disability. One of the main factors in selection of this group was severity, for in the early days of pioneer surgery only those whose prognosis appeared hopeless were given this chance of improvement; and even later, when the operation had proved itself, we were still selecting severe cases both from necessity and in order to establish the limits of the operation. Heart size alone indicates this, for of the

45 patients 12 had a cardiothoracic ratio of 60 or over, and 5 of over 65, the largest being 70. Eighteen patients were in atrial fibrillation and 27 in normal rhythm at the time of operation. There were 31 women and 14 men, a female preponderance that has continued in our series and in others reported. In presenting the follow-up of these 45 first cases it is important to stress that there was no selection of good operative risks or of those who might be expected to get the maximum improvement from operation; it was often the opposite.

THE FOLLOW-UP

First Three Years

The assessment of the total 45 patients over the first three years is shown in the Chart. We have used a change in grades of disability to classify results as excellent, good, fair, or poor, as shown on the left of the Chart. In the follow-up we have been more critical than the patients in assessing their state, and have not relied entirely on functional ability; thus, the onset of fibrillation or alteration in physical findings such as heart size has reduced a patient a grade even if there has been no decrease in activity or increase in symptoms. We have attempted to allow for the mentality and spirit of the individual patients in making an objective assessment, for while most patients make the best of any improvement in health there are a few who will always complain. In this respect, it should be remembered that our early patients had the spirit, and optimism, of pioneers.



Follow-up of 45 patients for three years. The large blocks show the total assessment at the end of each year; the small blocks the individual patients; the arrows show those patients who lost ground during the follow-up.

The first assessment was made after one year, when the psychological effect of surviving an operation on the heart had to a large extent disappeared, and every patient had experienced one autumn and winter, which are the proper seasons to assess disability from mitral stenosis, either before or after operation. During that year there was one death—a suicide following a seemingly poor result; six were disappointing—five having a fair result or one grade of improvement only, and one having a poor result with no improvement. The majority, 38 out of 45, were classed as good or excellent results.

During the second year four patients lost ground and two died; three of these six dropped from the good class, and one dropped from the excellent to the good class, so that there were 35 of the 45 with good or excellent results at the end of the second year. In the third year two patients showed further deterioration—one of them dying—and nine more patients lost ground, so that the number left with good or excellent results was 29 out of the 45 at the end of three years.

Thus, of the 45 patients who had survived operation, 4 had died and 12 had lost some of their original improvement and five of these were as incapacitated as before operation. Three of the deaths were in patients who had been assessed from the beginning as poor or fair results and were to be expected. The fourth, however, occurred in a patient (G8) who had been classed as a good result; she had aortic stenosis as well as mitral stenosis, but returned to a full life following mitral valvotomy; at the end of her second year, however, she went into failure with the onset of atrial fibrillation, and died as the result of quinidine therapy (Trounce and Finnegan, 1954, Case I). The reason for her unexpected deterioration was established at necropsy, which showed that her mitral valve was once more tightly stenosed, but her death was premature. Of the 12 who lost ground, one was assessed as only a fair result at the end of the first year, but the other 11 were all assessed as good or excellent results. The diminishing proportion of patients still remaining in the good or excellent class over the three years is shown in the Chart, for 4 out of 38 lost ground in the second year, and 9 out of 35 in the third year. The numbers of good and excellent results dropped from 38 to 35 to 29 at the end of the first, second, and third years, and if this steady drop continued at the same rate there would be few good results after another five years. The follow-up, however, of a smaller number of patients over a longer period does suggest that the effect of valvotomy is likely to be more permanent.

After Three Years

Nine of the 29 patients with good or excellent results at the end of three years have been followed for a longer period. At the end of the fourth year two had lost ground and two remained as good and five as excellent results. There are three patients completing five years of follow-up; two remain excellent results, while the third is our first patient operated on over six years ago, who deteriorated from an excellent result to a fair result in the third and fourth years, and has remained a fair result in the fifth and sixth years.

The state of the 45 patients who have been followed up through the varying period of three to six years, as judged by their assessment at the end of their first year, is given in Table I. It shows that, of seven whose immediate result was disappointing, four died and in three the result remained fair, whereas of the 38 whose immediate result was gratifying only one had died, 13 had lost ground, and in 27 the result remained good or excellent. This shows that, although the preliminary assessment on functional improvement gives an indication of prognosis, the future of the individual patient will vary greatly, and a good result from mitral valvotomy is a relative term which needs continued and critical assessment.

Table I.—*Comparison of Results One Year After Valvotomy With Assessment During and at the End of Follow-up Period*

	At End of One Year	During Follow-up			At Present
		Died	Lost Ground	Unchanged	
Dead ..	1	—	—	—	5
Poor ..	1	1	—	—	5
Fair ..	5	2	—	3	8
Good ..	17	1	7	9	12
Excellent ..	21	—	6	15	15

With this object various factors that influence the success of mitral valvotomy and the subsequent course are con-

sidered with relation to the findings and follow-up of the 45 patients. The factors considered are the degree of pulmonary hypertension, the state of the valve before valvotomy, the state of the valve after valvotomy, mitral regurgitation, atrial fibrillation, and rheumatic activity. The degree of disability, heart size, and the presence or absence of fibrillation before operation, although factors that may increase the risk of operation, have not appeared to influence the progress after operation.

In addition a detailed comparison is made between the group of 15 patients who have remained as excellent results throughout the period of follow-up and the group of 14 patients whose original assessment of good or excellent has had to be revised owing to subsequent deterioration.

DETAILED STUDY

Degree of Pulmonary Hypertension

In Table II the degree of success from operation is related to the degree of pulmonary hypertension before operation. The patients are divided into four groups showing moderate,

TABLE II.—*Average of Improvement Compared With Pulmonary Pressure*

	Mean P.A. Pressure in mm. Hg			
	–30	31–50	51–80	80+
No of patients	7	19	13	6
,, ,, deaths	1	1	0	3
Average degree of improvement in grades	1·0	1·8	2·5	1·2

marked, severe, and extreme pulmonary hypertension, as indicated by mean pulmonary artery pressures at rest. The grades of improvement, from 0 to 4, of each individual at the end of the follow-up period are totalled and divided by the number in each group, to give an average degree of improvement. The number of deaths in each group is shown because three of the five deaths happen to be in the small group of six with extreme hypertension, so that the average grade of improvement is greatly affected; for the other three patients in this small group it is 2.3, which is comparable with the larger group showing severe hypertension. There were reliable readings of "pulmonary capillary" pressures with which to calculate pulmonary resistances in only 21, or less than half the patients. In 13 patients with resistances under 500 dynes/sec./cm.$^{-5}$ the average grade of improvement was 1.7 as compared with 2.0 in eight patients with resistances over 500. This trend is comparable to the findings in Table II using mean pulmonary artery pressures, which suggests that the greater the degree of pulmonary hypertension the greater the chance of success from valvotomy. That patients with severe pulmonary hypertension do well and maintain their improvement after valvotomy indicates that the secondary changes in the lesser circulation are not so permanent as was once thought, which is also borne out by the large falls of pressure in post-operative readings in the best results (Table III).

TABLE III.—*Mean Pulmonary Artery Pressures in mm. Hg Before and After Valvotomy*

Case	Pre-op.	Post-op.	Result*	Case	Pre-op.	Post-op.	Result*
G1	62	32	E	G30	24	20	F
G4	40	27	E	G31	46	23	E
G5	59	27	E	G32	41	20	E
G6	100	55	G	G34	33	15	E
G8	85	24	G	G35	49	31	G
G9	52	35	E	G38	35	20	G
G10	63	30	E	G39	55	30	E
G13	51	22	E	G42	44	30	E
G16	100	81	P	G43	75	30	E
G22	26	16	G	G44	55	30	G
G23	RV 31	RV 6	G	G46	52	20	E
G25	RV 32	RV 46	F	G55	81	35	E
G26	33	25	F	G58	35	18	G
G27	57	36	G	G59	80	30	E
G29	84	23	E				

* Assessment after one year expressed as excellent, good, fair, or poor.

The measurements in three patients, all early in the series, who have had more than one catheterization after operation, are of interest, and are shown in Table IV. The first two were catheterized one year before operation, so that their immediate pre-operative pressures may well have risen further, as they had done in the third; both had

TABLE IV.—*Catheterization Data in Three Patients Before and After Valvotomy*

Patient Date of Op.	Time	P.A. Pressure in mm. Hg	Rhythm	Cardiac Index (L./sq.m./sec.)	O_2 Saturation Mixed Venous Blood %
G1 16/9/48	1 yr. pre-op.	60 mean	Sinus	1·9	46
	2 mths. post-op.	32 ,,	,,	2·5	65
	3 yrs. ,,	40 ,, 48/29	,,	2·4	53
	5½ ,, ,,	26 mean 40/18	,,	1·9	53
G5 5/9/49	1 yr. pre-op.	59 mean	Sinus	2·3	58
	6 wks. post-op.	50 ,, 70/30	A.F.	1·5	54
	1½ yrs. ,,	30 mean 40/18	,,	2·0	65
G6 2/3/50	2 yrs. pre-op.	80 mean	Sinus	2·4	60
	1 mth. ,,	100 ,, 130/78	,,	2·7	45
	5 mths. post-op.	50 mean 68/42	A.F. Reverted with quinidine A.F. in 5th year	2·4	61
	4½ yrs. ,,	32 mean 40/26	A.F.	1·8	58

in fact deteriorated, the second having fibrillated and been in right-sided failure between the pre-operative catheterization and operation. In the first, G1, a drop in pressure was found shortly after operation, but in the second, G5, who appeared to have an equally good operative result, we were surprised to find no significant fall in pressure six weeks after operation. This patient maintained that he continued to improve until his maximum capacity was reached in one year, and this is confirmed by the pressure eighteen months after valvotomy, when his mean pulmonary pressure was halved, and both cardiac index and O_2 saturation had improved. It is probable also that the third patient, G6, had not reached his lowest pressure when he was catheterized as long as five months after operation, for the pressures were even lower four years later; the drop in cardiac index on this occasion may be significant, as he had not been so well in his fourth winter after operation and was found to be fibrillating and was not on digitalis; he was digitalized, catheterized, and then normal rhythm was restored once more with quinidine.

Both the first and third patients show that the initial drop in pulmonary pressure has been maintained four and a half years after valvotomy. In the second patient the gradual improvement and slow fall of pressure taught us to delay post-operative catheterization for a year after valvotomy in those who had much pulmonary hypertension before. This gradual fall in pressure, indicating a gradual readjustment of the pulmonary circulation following valvotomy, is clearly of great practical importance. Patients with much pulmonary hypertension and high pulmonary resistances are liable to have a difficult post-operative period and should be given a longer convalescence than those whose pressures are merely a reflection of the stenosis of the valve alone. These catheter figures merely illustrate what has been a common clinical observation with a large number of patients.

State of Valve Before Valvotomy

In Table V the patients are divided into four groups according to the maximum diameter of the valve as estimated before valvotomy, and the incidence of calcification and regurgitation is also shown. It will be seen that in 23, or over half, the mitral opening was estimated as 1 cm. in length, though 17 patients had more extreme stenosis, which indicates that there is a critical size below which patients are incapacitated enough to need valvotomy. Only

TABLE V.—*Average Improvement Compared With Size of Valve Before Valvotomy*

	Maximum Diameter of Valve			
	Less than 5 mm.	0·5 to 1 cm.	1 cm.	Over 1 cm.
No.	10	7	23	5
Calcification present	4	1	7	2
Regurgitation noted	3	1	5	5
Average degree of improvement in grades	1·7	2·6	1·8	0·4

five patients had a valve diameter above this critical level, and all were found to have associated regurgitation, so that their incapacity was clearly not so predominantly due to tight stenosis. By totalling the grades of improvement, from 0 to 4, of the individual patients and by dividing by the number in each group, an average degree of improvement is obtained. This is a crude method, but it indicates that better results are to be expected when the valve is at, or below, the critical size of 1 cm. in diameter. It is of interest, also, that the group of seven who had the best average improvement of 2.6, which is between a "good" and an "excellent" result, had the smallest incidence of calcification and regurgitation, both occurring in the same patient. Table V indicates roughly what would be expected, that patients who are likely to derive most benefit from valvotomy are those with "tight" and uncomplicated stenosis.

State of Valve After Valvotomy

In Table VI the 45 patients are divided into five groups according to the state of the mitral valve after valvotomy. To assess the state of the valve by the length of the aperture is only a rough method, for it is an elaborate functional

TABLE VI.—*Final Result in Follow-up, Compared With State of Valve After Mitral Valvotomy*

	State of Valve after Valvotomy				
	Poor (Predominant M.I.)	Poor (2 cm. or Less)	Fair (Over 2 cm.)	Good (Over 3 cm.)	Excellent (Full Opening)
Total No.	3	7	17	10	8
Died	2	2	1	—	—
Poor result	1	1	2	1	—
Fair "	—	4	4	—	—
Good "	—	—	6	2	4
Excellent result	—	—	4	7	4

structure and not a simple diaphragm. From the detailed descriptions of the state of the valves made at operation this measurement, however, is an important and common factor that has the advantage of being expressed in figures.

The patients can, by using this factor alone, be divided fairly clearly into four groups, and the measurements given in Table VI were dictated by this, and not arbitrarily chosen. The detailed descriptions of the operation show why this is so. The group where the final measurement was under 2 cm. had rigid or calcified valves which would neither split along the commissures nor cut easily with a valvotome, and only a slight increase in a still rigid valve was achieved. The group with openings of 2 cm. or more were also difficult, and in few was it possible to get beyond the point of maximum stenosis (Brock, 1952), though the opening had been definitely enlarged and the mitral stenosis relieved. In the group with a final opening of approximately 3 cm. it had been possible to split or divide one of the two commissures, giving a wide opening and valve that was capable of good movement. In the fourth group, with an opening of over 3 cm. it had been possible to open both commissures, giving an opening of normal or nearly normal size and a good functioning valve. Three patients whose valve was so immobile after valvotomy that free regurgitation had resulted, although the stenosis was relieved, form a small and separate group. If the same general terms are used as in the clinical result, the operative results can be classed as poor, fair, good, or excellent, classing the three with regurgitation as poor.

When the patients grouped in this way are graded according to their subsequent course there is a close correlation between the degree of success of the operative result and the ultimate benefit. Of the 10 patients with *poor* operative results four died—two in the second year, one in the third year, and one in the fourth year; two patients were never considered to have improved more than one grade, but maintained their slight improvement; two patients who were thought to have had good results after one year lost all the improvement in the second year; and two deteriorated to fair results in their third year. Of the 17 patients with a *fair* operative result, only 10 had good or excellent results after the period of follow-up; one patient, who had a poor result, committed suicide three months after operation, one patient had a fair result and has maintained that improvement; seven patients, however, who were considered to have good results at the end of the first year lost ground subsequently, two of these returning to their state before operation—one in the third and one in the fourth year. Of 18 patients with *good* or *excellent* operative results, all but one remain in the good or excellent class; one patient was moved from excellent to good owing to the onset of fibrillation, though his capacity was unaltered; one patient, however, lost all her improvement in her third year during pregnancy, when heart failure occurred with the onset of fibrillation.

Early in our experience of valvotomy the two physicians found that when the surgeon was satisfied with what he had been able to do at operation there was little cause for anxiety in the post-operative period, and generally the physicians would be satisfied with the result. The evidence shown in Table VI, and summarized above, shows that time has not only confirmed this early experience but has reinforced the prime importance of what is actually done at operation. We now see that in some instances where early clinical assessment as well as catheter findings after operation have indicated a good result, the reason for later disappointment can be found in the surgeon's description of what he had been able to achieve and the state of the valve after valvotomy. The practical importance of this cannot be overstressed. The statement that mitral valvotomy was done successfully on such a date means little, and gives no indication of the future benefit to the patient, unless the surgeon has made at that time a detailed description of what he has actually done. Without this it will also be impossible to decide whether it is reasonable to attempt a second operation; this was done in three of our patients, and a more complete valvotomy was achieved. In this present study the assessment of the operative result has been made later, and independently, by one of the physicians from the detailed description dictated by the surgeon immediately after the operation.

The diseased mitral valve is a more complex and variable structure than the diseased stomach, and the alteration in its function which the surgeon is able to achieve by operation will vary much more than, for example, after a gastrectomy. Although the surgeon does not see the valve, mitral valvotomy is not a blind operation, and the experienced operator will be able to give a detailed description of the functioning state of the valve before and after operation, which is even more important than pressures taken at the time. Without this, the value of mitral valvotomy in mitral stenosis, and its help to the individual patient with the disease, cannot be assessed.

Mitral Regurgitation

In 14 of the 45 patients some degree of mitral regurgitation was noted by the surgeon before valvotomy (Table VII); in nine it was of mild degree and stenosis greatly predominated; in five it was more obvious, and the functional failure of the valve was due to a combination of stenosis and regurgitation; in no instance was it thought that regurgitation predominated over stenosis.

Regurgitation was found rarely in valves with the smallest openings and more commonly with the larger openings

TABLE VII.—*Incidence of Mitral Incompetence Before and After Valvotomy*

	No.	Died	Poor	Fair	Good or Excellent
Significant regurgitation found before valvotomy	5	2	1	—	2
Insignificant regurgitation found before valvotomy	9	1	1	3	4
Regurgitation produced by valvotomy	6	—	2	1	3
No regurgitation before or after valvotomy	25	2	2	4	17

(Table V). Thus, in the 10 patients whose largest diameter was less than 5 mm., there were three with mild regurgitation and all had calcification of the valve, it being extreme in two of them. In the seven patients with the diameter between 0.5 and 1 cm. there was one with marked regurgitation and gross calcification (G5, Fig. 7 in our original report). In the 23 patients with the diameter of the valve about 1 cm.—almost exactly half of the patients—there were five with regurgitation, and in one with extreme calcification it was considerable. In the five patients with a diameter exceeding 1 cm., all had regurgitation and it was marked in three; one of these had a moderate and one gross calcification.

The association between calcification and regurgitation is close. In 14 patients in whom regurgitation was found at operation calcification was present in nine. In those in whom regurgitation was associated with extreme stenosis it was a constant finding, though the regurgitation was mild in all but one; in those with less severe stenosis it was not a constant finding, and in the one patient whose diameter was 2 cm. it was absent. Of the 31 patients in whom no regurgitation was found at operation, there were only five with calcification, and in only two of these was it severe.

As might be expected, the patients in whom regurgitation was found at operation did not fare as well as those with pure stenosis. Of the five with free regurgitation two died, in the third and fourth year after operation; and one is not improved, though she is still alive four years after operation. The first of these three had the most severe regurgitation with a 2-cm. opening without calcification; her stenosis was certainly relieved, for both commissures were split and she was given a full opening and showed some temporary improvement. The second had the common 1-cm. opening with severe calcification, and neither commissure could be divided; she showed no improvement and steadily deteriorated with signs of stenosis and regurgitation. The third patient with an opening of 1.5 cm. and only slight calcification was operated on while pregnant as she had had two previous attacks of pulmonary oedema; both commissures were opened, giving a valve diameter of 4 cm., but after improvement for a year with a successful delivery she deteriorated with clear signs of mitral incompetence and an increasing left-sided electrocardiogram; in her fourth year after operation, with a child to look after, she is more handicapped than before operation, but without it she might well have succumbed with pulmonary oedema. One patient with significant regurgitation and heavy calcification of the valve had a good result from valvotomy with an opening of 3 cm., and although regurgitation was not relieved the result has remained good for four years. All these patients had clinical evidence of regurgitation before operation, but in the fifth (G5) it was not suspected, and no systolic murmur had been heard; he had tight stenosis with a powerful jet through a heavily calcified valve; a successful valvotomy diminished but did not abolish the regurgitation completely, but he has had no clinical evidence of it since, and after five years is still an excellent result as regards his mitral stenosis, though he is now being treated for hypertension.

Of the nine patients with a minor degree of regurgitation, two had poor operative results; one with very tight stenosis, gross calcification, and extreme pulmonary hypertension had no functional improvement, and died two years later; one with equally severe stenosis and calcification but with moderate pulmonary hypertension had a fair result and has not deteriorated after nearly four years. The other seven had fair operative results, for in none was it possible to open one commissure completely, and regurgitation was relieved in one only by valvotomy; two patients had fair clinical results, three good results, one an excellent result, and one who had a good result for three years deteriorated to a poor result with fibrillation in her fourth year.

It will be seen, therefore, that mitral valvotomy is less successful in those with regurgitation, as this is more often associated with rigid or calcified valves; when these are found it is more difficult to achieve a full relief of stenosis, and they favour the perpetuation of regurgitation. When mild regurgitation is associated with stenosis the chances of good results and prolonged improvement are less than in those with pure mitral stenosis, but even with moderate regurgitation good results from relief of the stenosis are still possible. When mitral regurgitation is predominant over stenosis, valvotomy is, of course, contraindicated, and there is as yet no successful operative treatment for this condition.

There are five patients whose physical signs after operation suggest that mitral regurgitation was produced by valvotomy, though it was not diagnosed at that time. Three patients all had a good operative result and still have an excellent or good functional result in their fourth year, the clinical evidence indicating mild mitral regurgitation without significant stenosis. In the other two it was not possible to achieve a wide opening and the main diameters were 2.5 cm. only; both were thought to have good results initially despite murmurs indicating stenosis and regurgitation, but both lost ground in the second and third years; one developed atrial fibrillation after operation that could not be reverted; in the other the electrocardiogram became progressively left-sided until she lost her improvement in the third year with the onset of fibrillation.

It is not uncommon to hear soft systolic murmurs after valvotomy, and this is compatible with a good operative and functional result. It would seem important that those with a systolic murmur of grade 3 or louder should be watched for evidence of increasing left ventricular size or electrocardiographic preponderance, for even if their stenosis is relieved and does not recur it is possible that mitral regurgitation may cause deterioration later.

Atrial Fibrillation

The onset of atrial fibrillation is a landmark in the natural history of mitral stenosis, and is often a turning-point where deterioration or failure begins. Heart failure is a frequent result, and, though this is often temporary until controlled by digitalis, few patients are as active as before this change in rhythm. One would therefore expect that those who were still in sinus rhythm before valvotomy was needed would fare better after operation than those who had fibrillation; and that those with fibrillation as the result of valvotomy and returned to sinus rhythm either spontaneously or with quinidine might form an intermediate group. This expectation is not realized in these 45 patients, as is shown in Table VIII. There were 27 patients in sinus rhythm before operation; 14 of these developed fibrillation,

TABLE VIII.—*Comparison of Patients in Sinus Rhythm or Fibrillation*

Rhythm	Total	Maintained Improvement	Lost Ground	Died
Sinus before and after valvotomy	13	6	6 (3)	1 (1)
A.F. post-valvotomy; reverted to sinus	11	6	5 (5)	—
A.F. post-valvotomy; not reverted	3	—	2	1
A.F. before operation (attempted reversion in 3; all failed)	18	14	1	3

The figures in parentheses are the number who changed from sinus rhythm to fibrillation during the follow-up.

but 11 of them were returned to sinus rhythm, so that there were 24 in sinus rhythm after operation. Of these, only 12, or half, maintained the improvement that valvotomy produced; two of these had only fair results and 10 have remained in the good or excellent class; all have remained in normal rhythm, though two have had paroxysmal fibrillation. The three patients who developed fibrillation after operation and did not revert all lost ground. In comparison, of the 18 who were fibrillating before operation 14 have maintained their improvement, 13 of them in the excellent or good class.

This comparison is surprising, for one might expect that the group with fibrillation before operation were in a more advanced stage of mitral stenosis than those who were in normal rhythm, and that therefore they would do less well; certainly they seemed a less promising group, for in only three was reversion with quinidine attempted and in each case it failed. It is, however, the progress of the group in sinus rhythm that has, in contrast, been disappointing. The 13 patients who were in sinus rhythm before and after operation fared no better than the 11 who fibrillated after operation and reverted either spontaneously or with quinidine. Twelve of these 24 patients lost ground, and in nine of these twelve the results were considered good or excellent until they developed fibrillation—two in the second year, four in the third year, and three in the fourth year; only one patient showed evidence of losing ground before fibrillation occurred. In two of these patients no disability was noted with the onset of fibrillation, but they have been considered to have lost one grade of improvement and are now classed as good rather than excellent results; three deteriorated with the onset of fibrillation, one still remaining as a good result and the other two as fair results; three lost all their improvement as the result of fibrillation, one during pregnancy, and are now no better than before operation; one patient died in an attempt to restore sinus rhythm with quinidine.

The onset of atrial fibrillation in these patients in sinus rhythm has been a disturbing feature in this follow-up, for it is cases in this group which have not fulfilled our early expectations. In fact, of the 13 patients with good or excellent results who subsequently lost ground, nine did so because of this. Atrial fibrillation develops in the natural course of mitral stenosis. It is too early to say what the ultimate effect of mitral valvotomy on this natural course will be, but it is a reasonable assumption that a successful operation will put the patient back to an earlier stage of his disease, if this is progressive. Why, therefore, have this small group done less well than those who had already progressed to fibrillation before operation? Any explanation must be tentative, as the numbers are small. We have no evidence that continued rheumatic activity was a factor in the group. The heart size was on the whole smaller—average 53% in those with normal rhythm, compared with 59% in those with fibrillation—and there was no evidence of progressive enlargement occurring before the onset of fibrillation. There was no significant difference in the degree of pulmonary hypertension in the two groups.

One factor that might have an effect is the age of the patients, for it is known that the incidence of atrial fibrillation in mitral stenosis increases with age. The average age of the 18 patients who were in fibrillation before operation was 37, while that of the 27 who were in sinus rhythm was 30. The average age of the 13 who did not develop fibrillation post-operatively was 30, and that of the 11 who reverted either spontaneously or with quinidine was 32. Of the 24 patients who continued in sinus rhythm after valvotomy, the average age of the 15 who have remained in sinus rhythm through the follow-up is 30, while the average age of the nine who developed atrial fibrillation during the follow-up was 32. This does suggest that the age of the patient may be a factor in the onset of fibrillation after operation, and subsequently, and that valvotomy has not played much part in altering the natural history of the disease. Age alone, however, can hardly explain the fact that the group in sinus rhythm did not fare as well as those who were in fibrillation, nor the very striking and permanent deterioration that resulted in three of the patients when fibrillation occurred.

The factor that may well explain the difference in the two groups is the operative result. Of the nine patients in sinus rhythm with good or excellent results who lost ground with the onset of fibrillation, two had a poor, five had a fair, and only two had a good or excellent operative result as assessed in Table VI. In contrast, of the 13 patients who were fibrillating before operation, who were not reverted, and who maintained their good and excellent results, none had a poor, three had a fair, and ten had a good or excellent operative result. That the operation rather than the rhythm is the decisive factor is also confirmed by the fact that those who maintained good results in sinus rhythm had comparable valvotomies with those who maintained good results in fibrillation, and more successful valvotomies than those who did not remain in sinus rhythm.

It would seem, therefore, that in some of these patients we were too optimistic about the permanence of their improvement because they were still in sinus rhythm. Valvotomy had in effect produced an opening above the critical level enough to rid them of their previous mechanical* disability, and to return them to active life; their margin was, however, small, though an adequate flow through the valve was maintained while they were in normal rhythm; with the onset of atrial fibrillation, the loss of the small force of atrial contraction was enough to lessen or eliminate that small margin, and they therefore lost ground or reverted to their pre-operative state. The more active life they were able to lead may have been an additional factor. It is probable that the diminution of their margin of safety is a gradual one, though the effect is revealed by the onset of atrial fibrillation. This was well seen in one patient (G19), who remained without symptoms for three years until she began to get increasing pulmonary congestion when pregnant and the onset of fibrillation produced congestive failure. It is difficult to avoid the conclusion that there is gradual re-stenosis of the valve in these patients, and in the one who died after fibrillation the valve was found to be tightly stenosed.

Rheumatic Activity

The degree and duration of active rheumatic carditis are prime factors in determining the course of rheumatic heart disease and the wide difference in prognosis between patients who die early and those who have a full span of years despite clear evidence of past disease. Although rheumatic activity diminishes with the years, it is not uncommon to find evidence of smouldering activity or of more acute episodes later in life. The finding of Aschoff nodes in a remarkably constant proportion of left auricular biopsies by different observers suggests that active disease may be present even where clinical evidence is lacking. The importance of this possibility in the future of patients who have had mitral valvotomy is obvious, for recurrent episodes of rheumatic endocarditis might cause re-stenosis of the mitral valve or lesions in other valves and impair the power of the myocardium to compensate for them. This factor, even if an important one, might require a longer period and more cases than are included here before it became apparent.

We have diagnosed rheumatic activity in 8 of the 45 patients, in 1 of the 5 who died, in 3 of the 13 who lost ground, and in 4 of the 27 who have maintained their improvement after operation. This number is too small to give any clear indication of the importance of this factor after valvotomy, and it is therefore necessary to refer such evidence as we have to the individual patients.

Two patients were thought to have rheumatic activity following operation. In the first, a man of 33 (G18), post-operative fibrillation was not controlled by digitalis, his pyrexia did not respond to antibiotics, his heart size increased, and right-sided failure developed. After 14 weeks he returned home more disabled than before operation, and committed suicide seven weeks later. The report of the coroner's necropsy gave no adequate information to

*At

decide about rheumatic activity. A difficult post-operative period with congestive failure and pulmonary infarction is not uncommon in cases with much pulmonary hypertension, but in this patient there appeared another factor in his disappointing result, which we suspected, without proof, to be rheumatic activity. Had he not taken his life he might have weathered this period, for the other patient had an equally prolonged and difficult post-operative period. This man, with tricuspid disease and severe pulmonary hypertension (G58) gave clear evidence of pulmonary infarctions after valvotomy, which may well have been the explanation of his long pyrexial course and congestive failure, but at the time we thought that rheumatic activity might be present; he has had no evidence of it since.

There were nine other patients whose post-operative or convalescent period was disturbed by pain, usually left-sided, and pyrexia, often producing a transient failure. This appears to be the same syndrome as that described by Soloff *et al.* (1953) as a reactivation of rheumatic fever. Although at first our suspicions were roused, we do not now consider this fairly common occurrence as evidence of rheumatic activity. It is not confined to operations on patients with rheumatic heart disease, and we regard it as a non-specific reaction of the pericardium. We think, however, that this reaction does not wholly explain the post-operative course in these two men and that a diagnosis of rheumatic activity was justified on the clinical evidence. Patients may also notice recurrent chest pain for some years after mitral valvotomy. It is not associated with general symptoms and signs as in this pericardotomy syndrome, and there is even less reason for regarding it as evidence of rheumatic activity. Most patients look upon it as a minor mechanical effect of a successful operation and mention it only if asked; but it may be a troublesome symptom in those whose ill-health or temperament, or a disappointing operation result, gives them grounds for complaint.

Two women, aged 41 and 42, were suspected of recurrent rheumatic activity during the follow-up period because of episodes of peripheral joint involvement and malaise, though neither had typical rheumatic fever. Both were initially classed as good results; one had a difficult post-operative period with the syndrome already described; both had one probable episode of systemic embolism in the first year. Both returned to a full and active life. The first (G27), who was fibrillating before operation, lost all her improvement in the third winter after operation, with pulmonary congestion and pulmonary infarction. Continued rheumatic activity seemed clear enough here to suggest that re-stenosis of the valve had occurred, and this indeed was found when a second and more successful valvotomy was done at the end of four years. The second (G22) was in sinus rhythm, and her heart size had diminished after operation; despite the suspicion of rheumatic activity, she was very active, without symptoms or physical signs of stenosis, until the fourth year, when she suddenly lost all her improvement with the onset of fibrillation, and is now kept from right-sided failure only by medical treatment. Re-stenosis of her valve is possible, for neither commissure was split satisfactorily at operation, but the clinical evidence did not support this, and one is therefore inclined to suspect rheumatic myocarditis as a possible cause for her sudden deterioration.

The third patient (G1), aged 24, who in the four years following operation has shown some deterioration that we attribute to rheumatic activity, was the first patient operated on over six years ago. She had a good result until the third and fourth years, when she lost ground, and the result is now only fair. She has remained in sinus rhythm, and cardiac catheterization in her sixth year is substantially the same as after operation and better than before it; her valvotomy result, the physical signs, and electrocardiogram after operation were no more than satisfactory (Table IX), so it is possible that re-stenosis has occurred.* During her period of deterioration she has developed increasing signs of aortic disease, whereas previously these were minimal, and in her sixth year her heart size has increased. This evidence of progressive rheumatic heart disease, which may include re-stenosis of the mitral valve, suggests that rheumatic activity is present. Although embolism is rare after mitral valvotomy, this patient, like the two reported above, had a transient right hemiplegia in her fifth year.

In three other patients there was evidence of rheumatic activity in the follow-up years, but no sign that this has affected the result of operation. One of these had two frank attacks of rheumatic fever in her first year, but she has an excellent result, with no loss of ground in her fourth year after operation (G56).

The finding of Aschoff bodies in auricular appendages removed at mitral valvotomy has raised the question not only of the presence of rheumatic activity in the absence of clinical evidence but also the significance of these findings as an indication of rheumatic activity. The biopsies in our cases were reported on by Dr. J. B. Enticknap (1953) with his findings and conclusions in a larger series with necropsy controls; he is guarded concerning the significance of these findings, and has graded them as "probable" and "possible" evidence of rheumatic activity. In 37 of these 45 patients the auricular appendage was examined, 9 with "probable," 8 with "possible," and 20 with no suggestive evidence of any kind. There is no correlation between these findings and clinical evidence of rheumatic activity before or after valvotomy and the subsequent course in the follow-up years. Of the eight patients in whom rheumatic activity has been diagnosed on the evidence quoted above, it so happens that four were among the eight whose auricles were not examined; in only one of the other four was a "possible" lesion found, while the remaining three, including the patient with two attacks of rheumatic fever in the year following examination, had negative biopsies.

Comparison Between Those Who Maintained Improvement and Those Who Lost Ground

In order to establish criteria for a stricter assessment after operation a comparison was made between the 15 patients who maintained a good or excellent result for three years or more, and the 14 who were classed as having excellent or good results after one year, but who subsequently lost ground.

The second column of Table IX shows the number of years that a successful result has been maintained or the year when any deterioration was noted, with the degree of deterioration in brackets—that is, 2–D indicates death from a good result; 3–2 a change from excellent to good result. It will be seen that 5 of the 15 patients have maintained excellent results for more than the three-year period, and that 11 of the 14 who lost ground did so in the third year or later. This emphasizes the need for a long period of follow-up before it is possible to be confident about the success of valvotomy.

The third column is an assessment of the state of the valve after operation as previously shown in Table VI, the figure 1 corresponding to the valve where it was impossible to obtain a full split of both commissures leaving a maximum diameter of 2 cm. or less, and 4 corresponding to a full-size opening with both commissures opened. The fourth column is an assessment of the physical signs on clinical examination after operation, taking into account not only signs of mitral stenosis and regurgitation but involvement of aortic or tricuspid valves and clinical evidence of pulmonary hypertension; details of this complicated assessment would be tedious, but 4 indicates that evidence of any involvement of the mitral valve is difficult or impossible to find, whereas 1 would indicate not only clear evidence of mitral disease but rheumatic heart disease in its widest aspects. The assessment of the electrocardiographic evidence in column 5 is based primarily on evidence of right ventricular hypertrophy or atrial strain as shown in

*At a second operation, after completion of this paper, re-stenosis was found, but unfortunately she died the day after.

TABLE IX.—*Comparison Between Patients Maintaining and Losing Improvement After Valvotomy*

Excellent Results Maintaining Improvement

No. of Patient	Years of Follow-up	Valvotomy Result	Physical Signs	Electro-cardiogram	Heart Size (c.t.r.)
G4	5	3	2	3	63
G5	5	3	3	3	64
G10	4	2	3	3	59–56–60
G13	4	2	3	4	52–48
G21	4	3	3	4	54
G32	3	4	3	3	52
G34	3	3	2	3	68–70
G37	3	2	3	3	56
G39	3	4	2	2	70–62
G42	3	3	2	3	60–52
G43	3	3	4	2	61–56
G46	3	4	4	4	53
G55	3	4	3	3	55–47
G56	3	3	2	3	64
G58	3	2	3	3	67–62
Average	—	3·0	2·8	3·0	—

Excellent and Good Results Losing Ground

No. of Patient	Deterioration of Grade (and Year)	Valvotomy Result	Physical Signs	Electro-cardiogram	Heart Size (c.t.r.)
G1	3–1 (3)	2	1	1	56–60 (6th year)
G8	2–D (2)	1	2	2	58
G9	3–2 (3)	2	2	3	48–52
G19	3–0 (3)	3	2	2	57–55–61
G20	2–0 (3)	2	1	2	57–54–62
G22	2–0 (4)	2	4	3	63–59–63
G24	3–1 (3)	2	2	2	48–49
G27	2–0 (3)	1	1	2	49–50–58
G31	3–2 (3)	4	2	3	53
G38	2–1 (3)	2	2	3	52–53
G40	2–0 (2)	1	1	1	56–60
G47	2–1 (2)	2	2	2	58
G50	3–2 (3)	2	2	3	53
G52	2–1 (3)	2	2	2	56–64
Average	—	2·0	1·9	2·4	—

the P waves, the presence of atrial fibrillation or any indication of left ventricular hypertrophy lowering the patient one grade; thus 4 indicates a normal electrocardiogram in sinus rhythm with no evidence of mitral P waves, and 1 indicates evidence of right and left ventricular hypertrophy, and atrial fibrillation. The sixth column gives the cardiothoracic ratios, with any changes that have occurred in the follow-up, but does not indicate the diminution in size of pulmonary arteries and hilar markings, which were often seen where no overall diminution of heart size had occurred. The presence of organic disease of aortic or tricuspid valves, if significant, will affect the physical signs, electrocardiogram, and heart size.

In comparing the two groups it will be seen that those with maintained improvement had a better average for each individual assessment of operative result, physical signs, electrocardiogram, and change in heart size than those who lost ground. There is no emphatic difference in any one of the criteria, but the summation of all four points shows an overall difference in the two groups. Considering the advanced state of the patients who were operated on, one would not expect to find that a full opening could be achieved in each case with a resultant absence of clinical signs, a normal electrocardiogram, and a diminution of heart size. Nevertheless, one should be more hopeful for a more permanent result in those who show these more favourable points. Thus, in the first group, it would seem reasonable to expect a good future for patients 21, 32, 46, and 55, with a very successful valvotomy, with a minimum of physical signs after operation, and with small hearts. Patients 10 and 13, however, have equally good clinical evidence, but the valvotomy did not achieve a wide opening, and one is therefore more guarded about the future, though there is full functional activity after four years from grade 3, or severe incapacity, before operation. In contrast, patients 34 and 39 both have more obvious clinical signs, and large hearts from tricuspid disease, which may influence their future progress, though it appears that they have been successfully relieved of their mitral stenosis, with an improvement from total incapacity (grade 4) to slight disability (grade 1).

Patients who need mitral valvotomy differ so much in their clinical state before operation that one would not expect uniformity of findings in cases with equally successful results. Nevertheless, careful and continued assessment of all available data after operation is clearly important in judging the result and its possible permanence.

The importance of this is seen in the second group, who all had good functional results but lost ground later. It will be seen that, with two exceptions, a very successful valvotomy was not achieved, that only one patient was completely relieved of physical signs, that a normal electrocardiogram was never obtained, and that there was a temporary decrease in heart size in only three. The post-operative physical findings are not as satisfactory as in the first group, and in patient 22 only did they compare with the improvements seen frequently in the first group; this patient had evidence of rheumatic activity, but this did not produce functional deterioration or a return of signs of mitral stenosis until she developed fibrillation in her fourth year; it is difficult, however, to avoid the conclusion that some re-stenosis has occurred, since the valvotomy was only moderately successful. Patient 27, who also had evidence of rheumatic activity, had actually re-stenosed; for this was found at a second operation, when a more satisfactory opening was achieved. This patient, like the others in the group, had obvious physical signs despite a good functional improvement, and it would seem that when these are present future deterioration is always a possibility unless a full opening of the valve has been achieved. The only patient in the second group who had a full opening was patient 31, but he was considered to have lost one grade of improvement owing to the onset of fibrillation, though he continued at full employment without digitalis or symptoms.

While detailing these contrasting post-operative findings in this small group, it is pertinent to give our impressions of the larger group who have not yet been followed up for so long a period. We are most optimistic about those we know have been given a wide and functioning valve by valvotomy. This optimism is fortified if there is an appreciable change in the physical signs towards normality. In those in whom the valvotomy is less complete we are less optimistic, even if the physical signs are improved, and are guarded in our prognosis if obvious physical signs remain, however dramatic the functional improvement may seem.

SUMMARY AND CONCLUSIONS

We are reporting the present condition of the first 45 patients who survived mitral valvotomy, all of whom have been followed for three years and some for up to six years. A year after operation there were 38 good or excellent results and only 7 that were disappointing. At the end of three years another 11 of the 38 had joined the disappointing group, leaving 27 good or excellent results. The third year after operation is evidently more critical than the first two years, but some patients who have been followed for four and five years have maintained their improvement and are leading active lives.

If we may add a less complete and more recent follow-up, we have 50 patients who obtained a good or excellent result and have been followed for three years or more. The results after three years are much better in those who were graded as excellent than in those who were graded as good some months after operation, showing that this clinical judgment was in general a valid one for the future. If, however, to make it easier to follow, we combine the good and excellent results, we can say that 38 (76%) of the 50 patients are still as good after three years and 12 have lost ground. Of these

12, 8 (16%) have lost much of their improvement and 4 (8%) have lost all of it, and 2 of these 4 have died.

A smaller number, 19 of the 50 patients, have been followed till the end of the fourth year, and again there was some loss of ground, though 15 out of the 19 have maintained their improvement. Two, however, have lost much of their improvement and two have lost all of it.

We have tried to analyse the influence of various factors on the lasting good results. Rather to our surprise, the size of the heart, the degree of disability, and the presence of auricular fibrillation before operation do not seem to influence the result in this three-year period, though they will no doubt do so in the long run, and fibrillation does increase the operative risk. Obviously, operation should be most successful when the mechanical defect is severe and the heart muscle relatively good, and measurement of the valve at operation shows that the results were better where it was less than 1 cm. in diameter.

The best correlation between a lasting good result and anything that we could assess at the time is with the surgeon's account of what he was able to achieve at the operation. Where he found it impossible to produce an opening that was as much as 2 cm. or where there was gross incompetence, there were no good results; where he was able to produce a full opening or one over 3 cm. there were 17 good results and only one that was poor; and where the valve size was intermediate, 2 to 3 cm., the results were intermediate.

Mitral regurgitation before valvotomy does not always prevent a good result, but even a slight degree of this reduced the proportion of good results and increased those where they were only fair. We thought that regurgitation was produced by valvotomy in 6 of the 45 cases, and in 3 of these the result was poor or only fair, but in 3 it seems unimportant so far. There was a close association between calcification of the valve and regurgitation.

Pulmonary hypertension is a reason for operation rather than a contraindication. We have not met an example where a successful valvotomy has failed to reduce it, and, in general, the greater the degree of pulmonary hypertension, the better the chance of a good result.

The occurrence of atrial fibrillation after operation is perhaps the most disappointing feature. Temporary fibrillation after operation when sinus rhythm is restored spontaneously or with quinidine does not seem to influence the outlook, and these patients behaved in the same way as those who kept normal rhythm all the time. Paroxysmal fibrillation is not uncommon after any thoracotomy, and in some cases it may be of this type. In three patients fibrillation occurred after operation and normal rhythm could not be restored: all these three have done badly, but the numbers are small and we have seen other examples where this is not true.

We are surprised that those who had fibrillation before operation have actually done better in maintaining the improvement gained by valvotomy than those who had normal rhythm before, for 14 of the 18 have maintained good or excellent results. The onset of atrial fibrillation is to some extent a test of the heart's capacity, and unless the heart was able to stand this reasonably well, thus showing some reserve capacity, we may have regarded a patient as too ill to be suitable for operation; also loss of improvement from operation when atrial fibrillation occurs later indicates that the margin of benefit conferred was not great, and suggests that the valve has re-stenosed.

The prognosis in a young patient depends mainly on whether he receives further cardiac damage by further rheumatic infection. This is less true in older patients, but still has some relevance. We have little evidence, so far, that this is so in our patients. There is no correlation between the presence or absence of Aschoff bodies in the auricle and the clinical evidence of rheumatic activity and the subsequent course of the patients. But there is evidence in three patients, of whom one died and two had second operations, that there was some re-stenosis of the valve, which was more likely due to further rheumatic infection than to fibrosis from stress.

The so-called post-commissurotomy syndrome is, in our view, badly named, and is not specific to these cases. It should be called the pericardotomy syndrome, for it occurs after the pericardium has been opened for pulmonary valvotomy or other procedures as well as for mitral valvotomy.

We have compared in some detail the patients who have maintained their good results with those who have lost them. This difference correlates best with the surgeon's assessment about how much he was able to do with the valve at operation. Although at first the patient's symptoms and increased capacity are more important than any diminution in the physical signs, the latter give a better indication that the good result is likely to be lasting, and improvement in the electrocardiogram or radiograph is also of value.

If, finally, to summarize the prospects of a good result lasting, we may count two patients losing much of their improvement the same as one losing all of it, and even out irregularities, we can say that 2% of our patients lost all their improvement in the first year, 6% in the second year, 10% in the third year, and perhaps 15% in the fourth year. Although this shows progressive deterioration as the years pass, it is better than a preliminary estimate made a year ago, and may become better as more patients are followed. But it is unlikely that improved selection and improved surgery will ever prevent some progressive deterioration, for the operation —unlike that for a persistent ductus—is dealing with a heart that has been damaged by rheumatic infection.

It is pertinent to stress that this is a follow-up of our *first* 45 patients. These early patients were selected because of their bad prognosis, and some were operated on before the technique of mitral valvotomy was perfected. That all the patients have not maintained their initial improvement is not surprising, but even these have had the benefit of increased or normal activity for a year or more. That second operations can be done on some patients if re-stenosis occurs emphasizes the need for a careful and thorough follow-up.

We are grateful for the co-operation of many colleagues in this work, but particularly to Dr. H. E. Holling and Dr. A. Venner for their catheter studies; and to Miss N. Stapleford for her most valuable secretarial help.

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INFLUENZA VIRUS C INFECTION IN ENGLAND

BY

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In 1947 virus was isolated by Taylor (1949) from the throat washings of a man in New York who was suffering from a mild influenzal illness. It resembled the influenza viruses but differed from types A and B antigenically. Francis *et al.* (1950) later reported the recovery of a similar organism from the throat of a patient also suffering from an influenzal illness, and found serological evidence of infection in a number of other cases. They suggested that the new virus be known as influenza virus Type C, and this designation has been generally accepted (Taylor, 1951; W.H.O., 1953).

Isolations of influenza virus C have since been reported from other laboratories in the United States (Gerber *et al.*, 1952; DeMeio *et al.*, 1955) and from Japan (Fukumi *et al.*, 1951) and Czechoslovakia (Styk, 1954). However, few illnesses accompanied by an increase in antibody to this virus have been reported, and Minuse *et al.* (1954), commenting on experience at Ann Arbor, Michigan, stated that "continued search has yielded only a few additional cases." Studies of the distribution of antibody to influenza virus C in American population groups were made by Hilleman *et al.* (1953) and Davenport *et al.* (1953). These surveys showed a sharp rise in the general level of antibody during childhood, particularly in the earlier years. It seems probable that, in the United States, influenza virus C infection occurs widely in young children and may be accompanied by minor respiratory illness. Our own findings and those of Grist (1955) suggest that the same may be true in Britain.

In the course of a number of investigations during the past three years we have had an opportunity to make clinical and laboratory observations on the presence of influenza virus C infection in this country. Histories of illness were studied in persons whose sera showed antibody changes, and sera from these investigations were used to estimate the age distribution of antibody in the population. Cases of influenza virus C infection were found during three investigations. In the winter of 1952–3, 455 factory workers who had volunteered for an influenza vaccine trial were under observation in Luton, Bedfordshire (McDonald and Andrews, 1955). Eighty-two persons with an acute respiratory illness causing absence from work were visited at home. Specimens were taken from 63 of them for laboratory examination, and serological evidence of virus C infection was found in one (Table—Case 1). In the following winter approximately 50 volunteers from each of five factories in widely separated parts of the country were bled at monthly intervals and their respiratory illnesses noted. Evidence of infection was found in one volunteer (Table—Case 2). In a study of 25 families in Wembley, Middlesex, between November, 1953, and April, 1955, a clinical record of all respiratory illnesses was kept, and blood taken from the adult members at approximately three-monthly intervals. Throat swabs or throat washings for virus isolation were obtained in all febrile illnesses, and in adults additional blood specimens were taken to provide paired sera for any such illness. Laboratory evidence indicated that influenza virus C infection occurred in eight persons during this study (Table—Cases 3 to 10).

Sera for the estimation of age distribution of antibody were obtained from three main sources. Sixty-four out of 75 specimens from children aged less than 5 years had been taken from healthy individuals participating in a whooping-cough vaccine trial at the end of 1952. The remaining 11 sera in this age group and 25 specimens from persons aged 5 to 9 years were received at the Virus Reference Laboratory for various tests in the winter of 1954–5. Six hundred and seventy-seven specimens from 195 persons aged 15 to 64 years were from the 1953–4 factory investigations mentioned above. All specimens of serum were stored at −15° C. or −30° C. until tested. Most specimens for virus isolation were stored at −70° C., but a few which were tested within seven days of collection were kept at +4° C.

Laboratory Methods

The haemagglutination-inhibition (H.I.) test was performed in a cold room at 4° C., using plastic haemagglutination plates (W.H.O., 1953). The antigen consisted of amniotic fluid from fertile hens' eggs infected with influenza virus C strain 1233 obtained from Dr. A. Isaacs, of the World Influenza Centre. Eight partial haemagglutinating doses were used in the test.

The complement-fixation (C.F.) test was performed in the same plastic plates used for the H.I. test. Serum, complement (2½ M.H.D.), and antigen were mixed in 0.1 ml. volumes, incubated at 37° C. for 75 minutes, and 0.2 ml. of a 1% suspension of sensitized sheep red cells was added. After 30 minutes at 37° C. the plates were stored overnight at 4° C. and results read next morning. Titres recorded were the highest initial serum dilution showing approximately 75% of red cells unlysed. The antigen, consisting of amniotic fluid from fertile hens' eggs infected with strain 1233, was used without purification, at optimum dilution. A buffered saline diluent containing added calcium and magnesium (Fulton and Dumbell, 1949) was used throughout the C.F. test.

Similar methods were employed for the serological diagnosis of influenza A and B, except that the H.I tests were performed at room temperature and in the C.F. tests standard preparations of soluble antigen were used.

Material for virus isolation was tested by the inoculation of 0.1 ml. into the amniotic cavity of six fertile hens' eggs on the 10th day of incubation. After three days' incubation at 35° C. the amniotic fluids were tested for ability to agglutinate fowl red cells at 4° C. The virus type was confirmed by complement-fixation, using dilutions of egg material against low dilutions of serum from persons convalescent after influenza virus A, B, and C infections. Small quantities of serum from a known case of influenza C infection were kindly supplied by Dr. Elva Minuse, of Ann Arbor, Michigan. All specimens for virus isolation were given at least two egg passages.

Case Reports

Laboratory evidence of recent infection with influenza virus C was found in eight adults and two children; a summary of observations made on them is given in the Table. In the eight adults a fourfold or greater rise in antibody between two bleedings was observed by C.F. or H.I. test, or both. In some of these both titres were low,

but, as a fourfold or greater rise was demonstrated to influenza virus C and not to virus A or B, they are included. In two of the eight adults—Cases 1 and 10—the first blood specimens were taken in the acute stage of an influenza-like illness, mild in one and moderately severe in the other. The second specimens in these two cases were taken 20 to 23 days after onset. Virus isolation was attempted without success on throat washings collected within three days of onset from both these patients.

The two children (Cases 6 and 7) were sisters, and, together with their elder brother aged 13 years, developed a severe running nose on the same day. A throat swab was taken from the youngest child (Case 6), who had a rectal temperature of 99° F. (37.2° C.) and a moderately severe cough when seen on the day after onset, and virus C isolated from it. The specimen was taken with a wooden-shafted swab and the end broken off into a screw-capped bottle containing broth. It is interesting that this specimen was kept at 4° C. until inoculated into eggs four days later and not at −70° C. as was usually done. Blood samples were taken from the three children and from their mother and father 18 days after the onset of illness in the children. The parents, who had been bled three weeks before the episode and again four months later, had no illness of any kind during this period and showed no serological changes. The two sisters had antibody titres of 1/256 and 1/512 to influenza virus C complement-fixing antigen, strongly suggesting recent infection, but that of their brother was less than 1/2.

In the remaining six patients shown in the Table a fourfold or greater antibody rise was noted between two routine bleedings. In Case 2 the gap between the bleedings was five weeks, and it seems possible that the rise was associated with a common cold which occurred seven days before the second bleeding. It was the only illness during the period. The time interval between specimens in the other cases ranged from three to five months, and though all but one had colds in this period it is impossible to say whether the antibody changes were related to any of these illnesses. Certainly nothing more severe than a common cold resulted from the infection in these five persons.

It is perhaps worth noting that, though the 10 cases shown were spread over three years, the serological changes occurred during the first half of the year in eight of them. It is possible that the same was true of the other two cases, but in these the interval between bleedings was long, the specimens being taken in April and October. The significance of a trend based on so few observations is obviously questionable.

Age Distribution of Antibody

It is not claimed that the 295 subjects from whom blood was available for study of age distribution of antibody were necessarily representative of the population of this country. The great majority were, however, normal healthy persons from widely separated towns. The sera in the 5–14-year age group were least satisfactory, as they were from persons suffering from some febrile illness.

The proportion of sera with a complement-fixing antibody titre of 1/10 or higher in each age group is shown in the accompanying Diagram. A titre of 1/10 was chosen because approximately half the sera from persons over 14 years of age were positive at this level and errors due to non-specific effects were unlikely to be great. The proportion positive rises steadily from a low level (5%) in those under 5 years to a peak (61%) in the 25–34-year age group and remains high thereafter. The fall in the proportion positive

Summary of Findings on 10 Patients from Whom Laboratory Evidence of Infection with Influenza Virus C was Obtained

Case No.	Sex	Age (Yrs.)	Dates Bled	Antibody Titres						Egg Inoculation	Date of Onset and Nature of Any Illnesses Associated in Time with the Serological Changes	Other Observations
				C.F. Test			H.I. Test					
				A	B	C	A	B	C			
1	M	47	30/1/53 18/2/53	1/8 1/8	1/4 1/4	*	1/10 1/20	*	1/30 1/120	Neg.	29/1/53: Typical influenza of moderate severity—shivering, sweating, aches and pains, irritating dry cough, "tight" chest, slight coryza. Temperature 98° F. (36·7° C.) on 30/1/53	
2	M	38	16/2/54 23/3/54	<1/5 <1/5	1/5 1/5	1/5 1/40	* *	* *	* *	*	16/3/54: Common cold	
3	F	31	30/1/54 25/4/54	<1/5 <1/5	<1/5 <1/5	<1/5 1/40	* *	* *	1/5 1/80	*	31/3/54: Common cold	Husband bled on same dates had no illness and no serological changes. Her 2 children, aged 6 and 4 years, had colds on 29/3/54 and 31/3/54 respectively
4	F	36	3/2/54 22/4/54	1/5 1/5	<1/5 <1/5	1/10 1/20	* *	* *	1/10 1/80	*	3/2/54: ,, ,,	Husband bled on same dates had no illness and no serological changes. Her 2 children, aged 6 and 3 years, had colds on 25/1/54 and 26/1/54 respectively. The younger child had a temperature of 99·4° F. (37·4° C.) (P.R.)
5	M	36	6/2/54 6/5/54	<1/5 1/5	<1/5 1/5	<1/5 1/10	1/20 1/20	1/20 1/20	1/10 1/80	*	No illness	Wife bled on same dates had a twofold rise in antibody to virus C but had no illness. The elder of their 2 children, aged 5 and 3 years, had a cold on 2/3/54
6	F	2	31/5/54	<1/5	<1/5	1/256	*	*	*	Virus C isolated	13/5/54: Febrile cold with moderately severe cough	These children were sisters; their brother, aged 13 years, had a cold on 13/5/54 and was also bled on 31/5/54, when his antibody titre to virus C was <1/2. Their mother and father had no illness at the time, and blood taken on 24/4/54, 31/5/54, and 2/10/54 showed no antibody changes
7	F	6	31/5/54	<1/5	<1/5	1/512	*	*	*	*	13/5/54: Common cold	
8	F	31	25/4/54 2/10/54	<1/5 <1/5	<1/5 <1/5	1/5 1/10	* *	* *	1/10 1/40	*	15/5/54: ,, ,, 3/7/54: ,, ,,	Husband, bled on same dates and on 24/7/54 in addition, had a febrile cold on 11/7/54, but showed no serological changes. Their children, aged 3 and 5 years, had colds on 8/5/54 and 12/5/54 and febrile colds on 5/7/54 and 4/7/54 respectively
9	M	17	25/4/54 2/10/54	<1/5 <1/5	<1/5 <1/5	<1/5 1/10†	* *	* *	<1/5 1/10	*	28/4/54: ,, ,,	Mother and father bled on same dates had no illnesses and no serological changes, and sister aged 6 years was not ill during the same period
10	F	40	15/2/55 9/3/55	1/5 1/5	<1/5 <1/5	1/5 1/10	* *	1/40 1/40	1/20 1/80	Neg.	13/2/55: Mild influenzal illness—aches and pains, cough, and "tight" chest. Not febrile	Husband, bled on 5/1/55 and 9/3/55, had no illness and no serological changes. Their children, aged 15, 4, and 3 years, were not ill during the same period

* Not done. † Serum slightly anticomplementary.

between 35 and 44 years is worth noting, though it may well have been due to chance. It seems reasonable to conclude that a high proportion—probably the majority of persons in this country—have encountered the virus at some time during childhood or early adult life. Our results give no indication of the extent to which infection was accompanied by illness nor the part played by reinfection in the maintenance of antibody levels. The fact that 8 of the 10 cases reported here were drawn from 7 out of 25 families observed for only 18 months suggests that infection with influenza virus C is not uncommon.

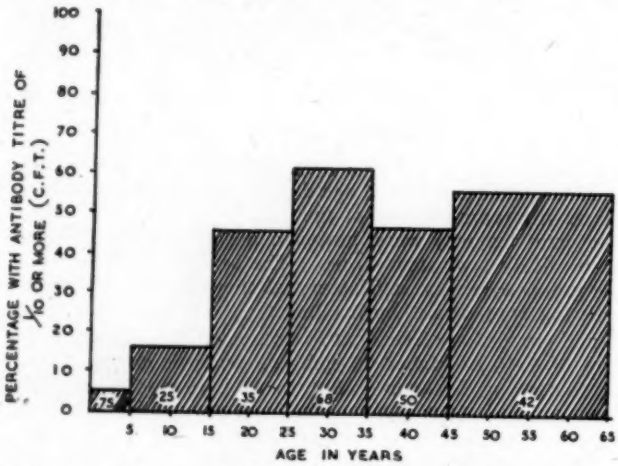

Diagram showing age distribution of antibody to influenza virus C. (The number of persons tested is shown in each age-group column.)

Summary and Conclusions

Ten cases are reported in which serological evidence of recent infection with influenza virus C was found. Influenza virus C was isolated from a throat swab of one—a girl aged 2 years suffering from a febrile cold and cough. Her sister, aged 6 years, had a cold on the same day and had a high antibody titre to influenza virus C 18 days later. A fourfold rise in antibody was found in paired sera taken from two adults suffering from a mild influenza-like illness. The remaining six cases had a fourfold or greater rise in antibody between two routine bleedings. Five of the six had colds during the period, but it is not known whether influenza virus C infection was responsible.

Blood specimens from 295 persons aged 4 months to 64 years from widely separated parts of the country were tested for complement-fixing antibody to influenza virus C. The proportion with an antibody titre of 1/10 rose from 5% in the 0–4-year age group to 61% in the 25–34-year age group and then remained high.

It is concluded that influenza virus C infection is common in this country and that infection may be responsible for acute respiratory illness.

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INFLUENZA A AND C IN GLASGOW, 1954

BY

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The studies of influenza in pneumonia which began in 1950 and were reported in previous papers from this unit (Grist *et al.*, 1952; Grist and Landsman, 1955) were continued in 1953 and 1954. Because of the particular importance of acute respiratory infections in the very young, and because of the possibility that influenza C virus might be a cause of such infections in the early years of life, the scope of the investigation was extended in two respects. Firstly, infants were included in the study in addition to adults. Secondly, tests for influenza C infection were made in addition to those for type A and B virus infections. The present paper describes the results of these investigations during 1953–4.

Material and Methods

The patients studied were those admitted to adult and baby pneumonia wards in Ruchill Hospital, Glasgow. The adults comprised those admitted to one female ward from October, 1953, to July, 1954, to one male ward from January to July, 1954, and to another male ward from February to May, 1954. Table I shows the ages and diagnoses of 145 cases admitted to these adult wards during the period February–May, 1954, when influenza infections were detected. The infants were an unselected series admitted to wards in which an investigation of respiratory disease

Table I.—*Ages and Diagnoses of Cases Admitted to Adult Pneumonia Wards During February–May*, 1954

Diagnosis	Age Groups (Years)				Totals
	7–19	20–39	40–59	60 and Over	
Pneumonia	7	10	30	28	75
Bronchitis	3	3	16	23	45
Other respiratory diseases ..	2	2	7	2	13
Non-respiratory ,, ..	2	4	3	3	12
Totals ..	14	19	56	56	145

in infancy was in progress. Of these, 70 were aged less than 1 year, and 23 were over 1 year but under 2 years old. The clinical aspects of their illnesses will be the subject of an independent communication. One serum specimen was taken from each patient as soon as possible after admission to hospital, and a second serum was obtained 7–10 days later, if possible. This paper describes only those patients from whom two such sera were taken, and whose second specimen was withdrawn not earlier than the tenth day of illness.

The 1233 strain of influenza C virus (Taylor, 1949) was supplied by the World Influenza Centre of the World Health Organization. This virus was passed by the amniotic route in fertile hens' eggs which had been previously incubated for 12 days. Antigens for complement-fixation (C.F.) and haemagglutination-inhibition (H.I.) tests consisted of pooled amniotic fluids harvested two days after inoculation with virus diluted 10^{-3} or 10^{-4}. Positive and negative control sera for these C.F. tests were kindly provided by Dr. B. E. Andrews, of the Virus Reference Laboratory, Colindale, from supplies received from Dr. Elva Minuse, of Ann Arbor, Michigan, U.S.A.

The C.F. technique employed 0.1-ml. volumes each of antigen (in optimal dilution determined by preliminary chessboard titration), serum dilution, and complement (two 100% haemolytic doses). Dilutions were made in saline solution. After standing at 4° C. overnight, the tests were allowed to reach room temperature before the addition to each tube of 0.2 ml. of 1% suspension of sheep cells sensitized with 5 M.H.D. of haemolysin. The tests were then immersed in a water bath at 37° C. for 30 minutes, and allowed to settle on the bench before reading. Conventional controls were included in each test. Sera giving positive C.F. reactions were usually tested against control antigen of normal amniotic fluid.

Virus for H.I. tests was titrated in half-step serial dilutions—for example, 1/2, 1/3, 1/4, 1/6—using 0.3-ml. volumes each of virus dilution and 0.5% fowl-cell suspension, allowing to settle for one hour at 4° C., and reading the patterns of settled cells. Vaccinia-sensitive fowl cells were employed, since the vaccinia-insensitive cells from one fowl were found to be relatively insensitive to haemagglutination by 1233 virus. Twofold serial dilutions of serum were made in 0.3-ml. volumes in plastic haemagglutination plates; to these were added 0.3-ml. volumes each of virus (four 100% haemagglutinating units) and cell suspension, and the patterns were read after the cells had settled for one hour at 4° C. Each batch of H.I. tests included a control titration of the virus dosage employed in the test.

For both C.F. and H.I. tests, sera were inactivated at 56° C. for 30 minutes in the initial dilution of 1/8 in saline solution. Adult sera were tested by both C.F. and H.I., but infant sera, which were usually available in small quantity and were required for other tests not described here, were usually tested by H.I. alone.

For the diagnosis of influenza A and B, infant sera were tested against "soluble" antigen preparations by a small-volume cold-overnight C.F. test like that described above. The usual method of fixation at 37° C. had been found relatively insensitive for testing infant sera (Grist, to be published). Infant sera were also examined by H.I. tests with the recently isolated virus strains A/Scotland/1/53 and B/England/52, and in a few cases with PR8 (type A) and Lee (type B) antigens also, using a technique similar to that described above for influenza C. Adult sera were tested by small-volume C.F. tests with fixation at 37° C. for 90 minutes, using type A and B "soluble" antigens (Grist and Landsman, 1955). All serum titres are cited as the reciprocals of initial serum dilutions.

Influenza virus isolations were made by the usual methods of amniotic egg inoculation. After incubation the extra-embryonic fluids were withdrawn and tested for haemagglutinating power against human Group O red cells at room temperature and against vaccinia-sensitive fowl cells at 4° C.

Results

The results of serological examinations are summarized in Table II. Nineteen influenza infections, evidenced by fourfold or greater increases in antibody levels to type A or C virus, were found during the period February–May, 1954. High levels of antibody, suggesting recent influenza infection, were found during a rather longer period. The proportion of pneumonia cases showing evidence of influenza was smaller than had been found during the previous

TABLE II.—*Results of Serological Examinations for Influenza Infection*

Period	No. of Cases Tested		Cases with Rising Titres				No. Positive without Rising Titre			
			Type A		Type C		Type A*		Type C†	
	A.	I.	A.	I.	A.	I.	A.	I.	A.	I.
Oct.–Dec., 1953	16	34	0	0	0	0	0	0	0	0
January, 1954	12	18	0	0	0	0	0	0	1	0
February ..	41	12	0	0	3	0	0	0	5	0
March ..	45	12	3	0	3	0	0	0	15	0
April ..	30	12	6	2	0	0	2	0	5	2
May ..	29	5	1	0	1	0	1	0	5	1
June ..	16	0	0	0	0	0	0	0	6	0
July ..	10	0	0	0	0	0	0	0	2	0
Totals ..	199	93	10	2	7	0	3	0	39	3

* Complement fixation titre ≥32
† C.F. titre ≥32 A./ or H.I. titre ≥64 } reciprocals of serum dilutions.
A=Adults. I=Infants.

three seasonal outbreaks (Grist and Landsman, 1955), and the notifications of death, respiratory diseases, and new sickness benefit claims from the Ministry of National Insurance gave little or no evidence of an epidemic during early 1954 (Weekly Returns of the Registrar-General for Scotland). Two strains of influenza A virus were isolated during the outbreak. The first was isolated from the lung of a 33-year-old woman who died of fulminating pneumonia in another hospital within two days after the onset of influenzal symptoms. The second strain was isolated from the throat of one of two infants who showed a rise in antibody titre to type A virus (Case 98, Table III). Both viruses were identified as Scandinavian subtype strains by Dr. A. Isaacs, of the World Influenza Centre.

As has been found during previous outbreaks (Grist *et al.*, 1952), evidence of influenza was not confined to any limited diagnostic category of patients admitted to pneumonia wards. Thus the diagnoses of 10 adults with type A infections included pneumonia (3 cases), bronchitis (4), febrile catarrh (1), asthma with emphysema (1), and cardiac failure (1). The two infants with type A infection had predominantly upper respiratory signs with cough, fever, and in one case radiological signs of bronchitis. The serological findings in these infants are shown in Table III: the antibody response was shown by the H.I. test with Scandinavian subtype A virus, and by the cold-overnight C.F. test with type A "soluble" antigen, but not by the C.F. test performed at 37° C. or by the H.I. test using the PR8 strain of influenza A virus.

Serological evidence of influenza C infection was found in seven adults. The main findings in these cases are shown in Table IV. The youngest was aged 45 years, and they suffered from a variety of illnesses. Upper respiratory symptoms were not recorded in the case histories of these patients, either before or after the onset of major illness. In every case, rising H.I. titres were shown with type C antigen, and in one case high levels persisted for at least two months. In five cases rising titres were shown by C.F. tests with type C antigen. Sera from two of these cases were tested with normal amniotic fluid control antigen and showed no fixation of complement. No sera from any of these cases fixed complement at 1/8 dilution with influenza A or B "soluble" antigens. The C.F. and H.I. tests were discrepant in two cases, in one of which anticomplementary sera rendered the C.F. test unsatisfactory and might have masked moderate antibody titres; in the other case, C.F. antibodies were not detected in 1/8 dilutions of serum.

TABLE III.—*Antibody Titres in Sera of Two Infants with Influenza Infection*

Case No. (and Age)	Date of Serum	C.F. Tests with Type A "Soluble" Antigen		C.F. Tests with Type B "Sol." Antigen (4° C.)*	H.I. Tests with Undernoted Antigens			
		4° C.*	37° C.†		A/1/Scot./53	PR8	B/Eng./52	C(1233)
94 (9 months)	7/4/54	<8	<2	<8	64	<8	8	64
	16/4/54	32	<2	<8	256	<8	8	64
	5/6/54	16	<2	<8	128	<8	N.T.	N.T.
98 (11 months)	11/4/54	<8	<2	<8	128	<8	N.T.	<8
	19/4/54	64	<2	<8	1,024	<8	N.T.	<8
	26/4/54	64	<2	<8	512	<8	N.T.	<8
	3/5/54	64	2	<8	512	<8	N.T.	<8
	19/5/54	32	<2	<8	256	<8	N.T.	<8

* Complement fixation at 4° C. overnight. † Complement fixation at 37° C. for 1½ hours. N.T. = Not tested.

TABLE IV.—*Findings in Adults With Evidence of Influenza C Infection*

Date of Onset	Age (Years)	Sex	Diagnosis	Day of Illness of Serum	C.F. Titres		H.I. Titres Influenza C Antigen	C.F. Titres with Soluble Antigens	
					Influenza C Antigen	Control Antigen		Type A	Type B
30/1/54	69	M	Bronchitis; coronary thrombosis (died)	11	<32 A.C.	<8 A.C.	<8	N.D.	N.D.
				20	<32 A.C.	<8 A.C.	32	<8	<8
3/2/54	63	F	Pneumonia (type 3 pneumococcal)	7	16	N.D.	64	N.D.	N.D.
				17	64	N.D.	256	<8	<8
Chronic	69	M	Pulmonary tuberculosis (died)	?	<8	N.D.	<8	N.D.	N.D.
				?+9	32	N.D.	32	<8	<8
7/3/54	45	M	Acute bronchitis	8	8	N.D.	16	N.D.	N.D.
				17	32	N.D.	64	<8	<8
24/3/54	53	M	Pneumonia (type 4 pneumococcal)	4	<8	<8	16	N.D.	N.D.
				14	16	<8	64	<8	<8
27/3/54	49	M	Pneumonia (type 2 pneumococcal)	4	A.C.	<8	32	N.D.	N.D.
				15	<8	<8	128	<8	<8
				100	<8	N.D.	64	N.D.	N.D.
2/5/54	52	M	Pneumonia (type 27 pneumococcal)	2	16	<8	16	N.D.	N.D.
				12	128	<8	512	<8	<8
				59	128	N.D.	512	N.D.	N.D.

A.C. = Anticomplementary. N.D. = Not done.

Among the infants no rising titres of influenza C antibody were detected by H.I. tests, and the distribution of titres differed greatly from that found in the adult group. Table V shows the distribution of antibody titres of sera from infants and from those adults who were investigated by both C.F. and H.I. tests. The results were obtained in tests performed at different times and with several batches of antigen. The figures represent individual sera; each patient generally contributed two sera. Excluded from the table are a few infant sera which caused non-specific agglutination of fowl cells, a few adult sera which were anticomplementary in the C.F. test, and sera from the seven adults with rising titres of antibody. The adult titres show a wide scatter in both tests, but with a tendency for high values in the two tests to be associated. By the C.F. test, 14% of adult sera gave titres of 16 or more, and 36% gave H.I. titres of 32 or more. Of the infant sera, 92% gave titres below 8 in the H.I. test, as compared with only 18% of adult sera with titres less than 8. Paired sera from four selected infants were tested by C.F. also. Four sera with titres of <8 by H.I. gave titres of <8 by C.F. also. Paired sera which gave titres of 64 by H.I. gave titres of 32 and 64 respectively by C.F. Paired sera which gave titres of 64 and 128 respectively by H.I. both gave titres of 32. Thus in infant sera also a positive correlation was observed between the results of the two tests with type C antigen. Despite the marked difference in distribution of antibody titres between the infant and adult groups, analysis of the adult titres by age groups showed no difference between the proportions of raised titres at different ages, but it is noteworthy that the youngest age group (7–19 years) included only 14 individuals.

TABLE V.—*Titres of Sera (Reciprocals of Serum Dilution) Tested for Influenza C Antibodies*

H.I. Titres	Adult Sera with Undernoted C.F. Titres				Total Adult Sera	Infant Sera
	<16	16	32	64		
<8	48	0	0	0	48	163
8	48	0	0	2	50	4
16	66	2	4	0	72	4
32	44	11	0	2	57	0
64	12	0	0	2	14	5
128	8	6	0	0	14	1
256	1	2	1	0	4	0
512	0	0	2	3	5	0
1,024	0	0	0	1	1	0
Totals	227	21	7	10	265	177

Discussion

The importance of influenza C virus as a cause of human diseases is uncertain. That this virus commonly infects man is indicated by the reports of Francis *et al.* (1950) and Taylor (1951) that H.I. antibodies were widely distributed among American adults; Kilbourne *et al.* (1951) found high titres of H.I. antibody in the sera of children aged from 6 to 14 years. In Britain, influenza C infection was first reported by Andrews and McDonald (1953), who now report several further cases associated with influenzal or coryzal symptoms (Andrews and McDonald, 1955). In the present investigation, antibodies to type C influenza virus were detected by both H.I. and C.F. tests. Despite a wide scatter, high titres by one test tended to be associated with high titres by the other, in both adults and infants. Interpretation of serum H.I. titres to the 1233 strain of influenza C is aided by the finding of Hilleman and Werner (1953) that human sera did not contain heat-stable non-specific haemagglutination inhibitor for this virus. In the present study, most infant and some adult sera failed at a dilution of 1/8 to inhibit haemagglutination by influenza C antigen, although many infant sera showed considerable (probably non-specific) H.I. titres with antigens of types A and B, particularly with the recently isolated strain A/Scotland/1/53.

The present study dealt with patients notified as pneumonia cases, who were not necessarily representative of the

general population of Glasgow. Nevertheless, the absence from most infant sera of demonstrable antibody to influenza C virus was in contrast with the frequent and higher titres found in the adults, and suggested that immunizing infections were common in early life. Of the three infants with H.I. titres of 64 or more, two were aged 9 months, and one was 15 months old; these high titres cannot be attributed to maternal transmitted antibody, but are likely to have been the result of infection. The only cases with rising titres of antibody indicating current type C infection were adults aged from 45 to 69 years. It is clear that infections by influenza C virus are by no means restricted to early life, as indicated also by the preponderance of 8 adults among the 10 cases described by Andrews and McDonald (1955). Although within the adult group increasing age was not found to be associated with an increased frequency of raised antibody titres, the very small numbers of individuals in the first two decades of the Glasgow "adult" series (Table I) may have obscured a trend of rising frequency of antibody during these years, as was found by Andrews and McDonald (1955).

The clinical diagnoses of the adults with type C infection were diverse and no common pattern of illness attributable to influenza C was detected. It should be emphasized, however, that these serological diagnoses were made retrospectively, and detailed histories to elicit information about influenzal prodromes or concomitants of the major illnesses were not specially taken from most cases. However, previous experience with cases admitted to pneumonia wards showed that type A and B influenza infections may also be associated with a variety of diagnoses, and that the influenzal component of illness may not be identifiable except by laboratory tests (Grist *et al.*, 1952; Grist and Landsman, 1955). Mixed epidemics of influenza due to viruses of different antigenic types are unusual, but not unknown. Thus a combined outbreak of influenza A and C infection was reported by Francis *et al.* (1950), and Kilbourne *et al.* (1951) described a mixed epidemic A and B. Despite the activity of both type A and C influenza viruses in Glasgow during early 1954, neither the city statistics of sickness and mortality nor the experience of colleagues in general practice suggested that a significant epidemic was in progress. The communal immunity to influenza A infection was probably high in 1954, as during the previous year Glasgow suffered a short outbreak of influenza due to Scandinavian subtype A strains of virus, and in winter 1950–1 a sharp epidemic of influenza A had affected the city.

Summary

Serological examination of adults and infants admitted to pneumonia wards in Glasgow showed outbreaks of infection by influenza viruses of types A and C during early 1954. Seven type C infections were diagnosed in adults, but none were detected among infants. The age distribution of antibodies suggested that most individuals in Glasgow are infected with influenza C during childhood.

I thank my clinical colleagues who supplied specimens and information used in this study. I am grateful to Dr. B. E. Andrews, of the virus Reference Laboratory, Colindale, and Dr. A. Isaacs, of the World Influenza Centre, Mill Hill, for initial supplies of influenza C virus and control sera.

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ADENOMATOSIS OF THE ISLETS OF LANGERHANS

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Since the earliest description of an insulin-producing tumour by Wilder *et al.* (1927), and the first surgical removal by Graham (Howland *et al.*, 1929) many cases of spontaneous hypoglycaemia due to islet-cell adenomata have been reported, so that Howard *et al.* (1950) were able to review 398 cases. Though from their comprehensive study it is evident that the adenomata were multiple (from two to ten) in 12.6% of the reported cases, it is of great rarity for a state of widespread adenomatosis of the islets to be encountered, and six examples only have so far been described.

The first was by Lang (1925) in a patient whose clinical story suggested hypoglycaemic attacks, though no blood sugars were recorded. An inoperable tumour mass was found in the pancreas, and on later section of the gland numerous yellow nodules 0.05–5 mm. in diameter were found and interpreted as islet-cell adenomatosis. Terbrüggen (1931) described a patient who died in hypoglycaemic coma, and whose pancreas showed widespread adenomata of the islets varying from 0.2 to 2 cm. in diameter. Howard *et al.* (1950) quote Engel (1942) as reporting one case, and Frantz (1944) published two cases, one of which had had two small adenomata removed at separate operations, before a subtotal pancreatectomy revealed widespread adenomatosis. In the second, two adenomata were palpated at operation, a subtotal resection was performed, and many microscopic adenomata were discovered, some of which appeared to have calcified. Of the 80 Mayo clinic cases of islet-cell tumour, one had a recurrence of symptoms after excision of a single adenoma, and histology of the tail of the pancreas, resected at a second operation, showed very numerous islet adenomata up to 1.5 cm. in diameter (Lopez-Kruger and Dockerty, 1947).

The following case is the first of its kind to be described in this country, and differs in several important ways from those previously recorded.

Case History

A woman aged 55 was admitted to the Midland Centre for Neurosurgery on May 20, 1954. Her early history was normal and the family history negative. She had three normal children.

For ten years prior to admission she had suffered a series of "attacks," which gradually increased in frequency and severity. At first she would develop a sudden weakness of the right leg while walking, which would recover within a few minutes and the attack not be repeated for two to

three months. Gradually the right arm also became involved, and for five to six years these episodes occurred at two-monthly intervals.

They then ceased and were replaced by sudden periods of loss of tone of the legs of very brief duration, so that she would fall to the ground but recover completely within a few minutes.

For the four years prior to admission the attacks had again changed, and they now occurred several times a week, consisting of periods of drowsiness, stupor, or coma, lasting from a few minutes to three hours, accompanied by deep respiration, yawning, copious salivation, and incontinence. Witnesses said that her lips and arms would twitch. Relatives thought these attacks were more frequent in the early morning or if she went without her meals, and stated that they could sometimes be prevented or shortened by taking food but had latterly occurred so often that she never ventured out of the house.

Examination showed that the patient was an alert and co-operative obese woman who responded normally to simple tests of intellectual function. Heart, lungs, and abdomen were normal, and repeated examination of the central nervous system showed no abnormality.

Investigations.—Radiographs of chest and skull were normal. Full blood count, C.S.F. analysis, blood urea, and urine were all normal. A prolonged glucose tolerance test was normal and fasting blood sugar was 90 mg. per 100 ml.; this rose in one hour to 140 mg. and in three hours had fallen to 90 mg. per 100 ml. Electroencephalography, carried out twice during the previous twelve months, showed only slight abnormality in the form of very occasional scattered 6–7 cycles-per-second waves.

Spontaneous Fits

Several fits were witnessed, and each showed a similar pattern. The patient seemed very confused on being roused in the early morning, and remained drowsy, unresponsive, and extremely restless for several hours. On several occasions there were twitchings of the face and hands, mainly involving the right side. During recovery the restlessness increased, she yawned frequently, and had no memory of her stuporous period. The blood sugar during one of these episodes was within the normal range, but several attacks were cut short by the administration of glucose.

Effects of Prolonged Starvation

The patient was therefore starved for 12 hours. The blood sugar fell to 40 mg. per 100 ml., and she became extremely drowsy and confused, recovering rapidly on being given oral glucose. Electroencephalography during the period of drowsiness showed gross abnormality, with high voltage, 1–3 c./s. waves in all areas, but particularly in the left-sided leads (Fig. 1). Episodes of this nature could be produced at will provided starvation was for more than 10 hours, and a blood sugar as low as 22 mg. per 100 ml. was once reported.

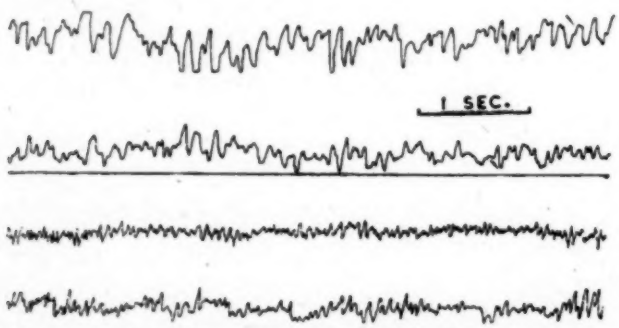

Fig. 1.—Upper E.E.G. tracing shows left parietal and left temporal leads during hypoglycaemic attack (blood sugar, 40 mg. per 100 ml.). Compare with lower tracing: same leads; tracing taken the following day, while normal.

Correlation of Serial Blood Sugars and E.E.G. Tracings

On another occasion, after starvation for 10 hours, she developed one of her typical periods of drowsiness and confusion. E.E.G. tracings at 11 a.m. showed gross abnormality, particularly in the left temporo-parietal leads, similar to the earlier tracing (Fig. 2, a). Blood-sugar estimations

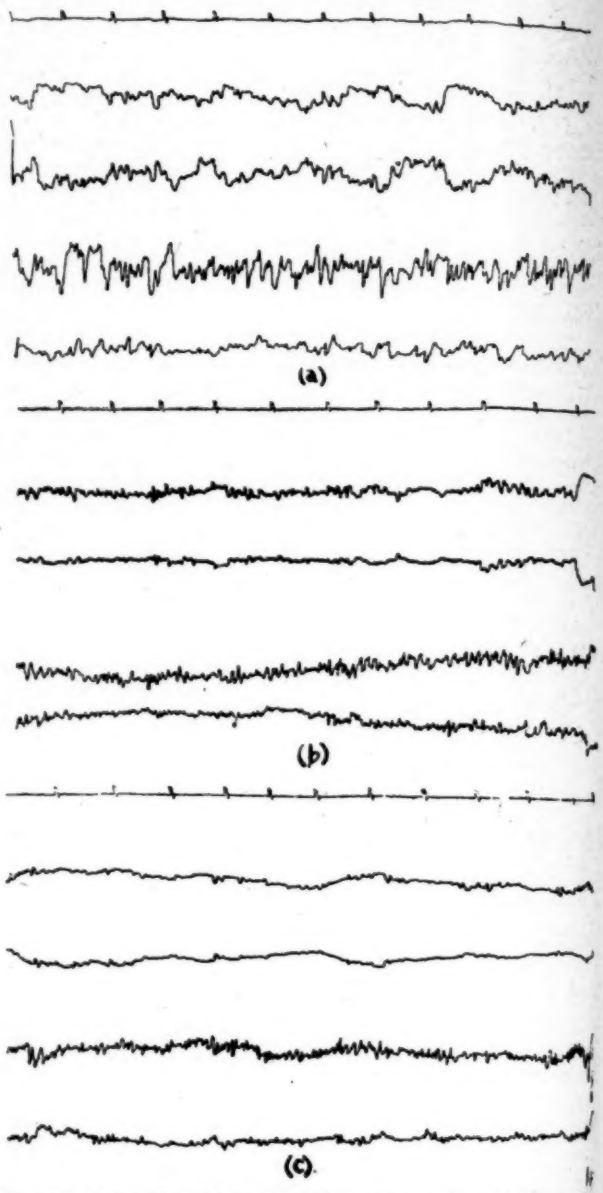

Fig. 2.—(a) E.E.G. tracing after 10 hours' starvation; blood sugar, 35 mg. per 100 ml. (b) 10 minutes after 30 g. glucose orally; blood sugar, 62 mg. per 100 ml. (c) 15 minutes after oral glucose; blood sugar, 78 mg. per 100 ml.

at 10.55 a.m., 11.30 a.m., and 11.45 a.m. gave readings of 35 mg., 40 mg., and 40 mg. per 100 ml. respectively. Glucose, 30 g., was then given orally. In less than five minutes the patient became extremely restless, throwing arms and legs about and making E.E.G. tracing almost impossible. In ten minutes she was quieter, the E.E.G. had become very much more normal (Fig. 2, b), and the blood sugar was 62 mg. per 100 ml.; in fifteen minutes the patient was normal, the E.E.G. practically normal (Fig. 2, c), and the blood sugar 78 mg. per 100 ml.

All requirements for Whipple's triad having been repeatedly obtained, a laparotomy was performed (by A. G.) on July 5, 1954. The pancreas *in situ* appeared to show no abnormality. A subtotal resection was performed, the tail

and the body of the pancreas being removed as far as the junction of the splenic and superior mesenteric veins, the spleen being excised in addition. Two nodules palpated in the excised gland were thought at the time to represent possible adenomata.

The patient's post-operative progress was satisfactory apart from a temporary hyperglycaemia. While controlling this with insulin she had a series of fits similar to those suffered previously. These were controlled easily by glucose, and on stopping the insulin ceased entirely; the glycosuria steadily decreased, and despite a chest infection she recovered completely.

Six months after operation she was better than at any time for the last ten years, had been entirely free from fits, and had a perfectly normal electroencephalogram.

Pathological Report

The resected portion of the pancreas, consisting of the body and tail of the organ, measured 11 cm. in length. It presented no abnormality to the naked eye. Two ill-defined areas of increased consistency could be palpated near the cut end of the specimen, but they did not correspond with the position of the adenomata subsequently discovered. Transverse sections of the pancreas for histological examination were taken at 1-cm. intervals along the length of the organ (see Fig. 3). Examination of these sections showed the presence of a great number of islet-cell tumours, varying in diameter from 0.2 to 7 mm. The distribution of the larger tumours is shown diagrammatically in Fig. 4, and the actual microscopical appearances of a representative section, H–H, in Fig. 5. It will be seen that, while the largest tumours lie on the surface of the pancreas, and within 5 cm. of the tail, many lie buried in the interior of the organ, and some are present in the section nearest to the head of the pancreas. In addition to the tumour-like masses of islet tissue, normal and hyperplastic islets are present throughout, but are too small to be shown in the diagrams. With one exception the tumours present a uniform histological appearance (see Fig. 6). They consist of anastomosing cords and, in places, rosette-like clusters of rounded or polygonal cells. The nuclei are small, round, or oval, and generally central. Here and there a nucleolus can be made out. The size and staining reaction of the nuclei show but little irregularity, and mitotic figures are very infrequent. The cytoplasm is clear and eosinophilic, and in a few areas shows a little hydropic change. It was not found possible to demonstrate any specific granules in the formalin - fixed material. The cell-columns are separated by a rich network of sinusoids. No ductules were seen in any of the tumours. The tumours do not possess a definite capsule, but are separated from the surrounding exocrine tissue by a delicate reticular network—as are normal islets. The surrounding acini do not show any evidence of compression or invasion; nor is there any sign of blood-vessel invasion.

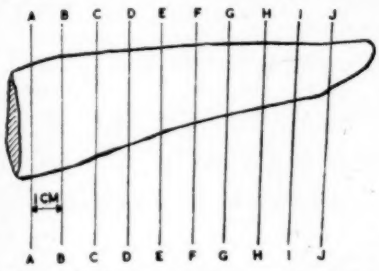

FIG. 3.—Diagram of body and tail of pancreas showing planes of section illustrated in Fig. 4.

FIG. 5.—Histology of section at plane H–H (see Figs 3 and 4). (×6.)

One tumour shows regressive change (see Fig. 5). In this, strands of surviving islet cells crisscross a hyaline mass of degenerated tumour tissue, which appears to have undergone ischaemic necrosis.

The histology of the tumours reproduces that of normal islets; they differ from the hyperplastic islets seen, for example, in the infants of hyperglycaemic mothers, or in some obese subjects (Ogilvie, 1933), by their very much larger size; by their number; and by their irregular size and distribution.

Discussion

The interest and importance of this case lie in the pathological findings. The clinical features corresponded to the now well-known picture of hyperinsulinism, and investigation

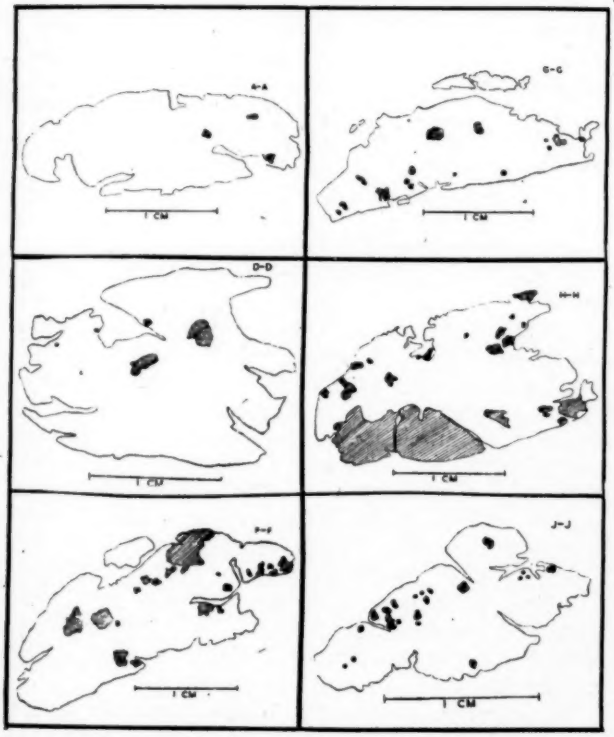

FIG. 4.—Diagrammatic representations of larger adenomata at six representative planes of section—see Fig. 3.

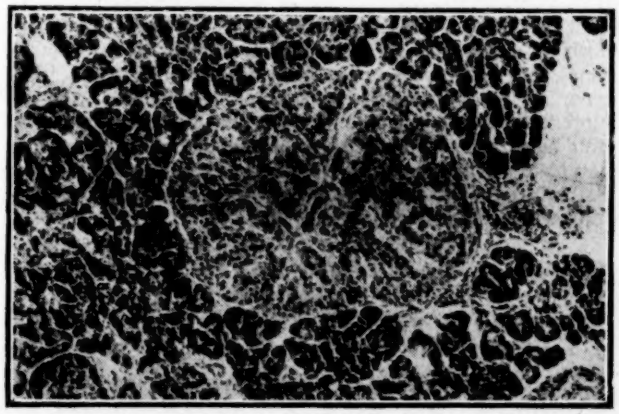

FIG. 6.—Higher-power photograph of one of the smaller adenomata, showing reproduction of normal islet tissue. (×85.)

repeatedly fulfilled Whipple's diagnostic criteria—(*a*) neurological disturbances occurring while fasting, (*b*) blood sugar below 50 mg. per 100 ml., and (*c*) rapid relief on the administration of glucose.

In all the previously reported cases of adenomatosis of the islets the condition has been discovered either at necropsy or after subtotal resection of the pancreas occasioned by relapse of symptoms following previous removal of single adenomata. Many authors, including Black *et al.* (1954) recently, stress the dark red or plum-coloured appearance of these neoplasms, and their firm consistency as compared with normal pancreatic tissue.

Our case illustrates, however, that a state of adenomatosis may exist without any visible or palpable abnormality in the pancreas at operation. Indeed, though immediate examination of the excised body and tail revealed two small palpable nodules, neither of these in fact corresponded to any of the adenomata later demonstrated. (Such areas can often be felt in the normal pancreas, and may be due to localized increase in the interlobular fibrous tissue.) Though histological examination showed some of the tumours to be on the surface of the pancreas, a great number were deeply embedded in the glandular tissue, and are very unlikely ever to have been palpated. Again, the adenomata in this case showed no distinct colour which might separate them from normal pancreatic tissue. It is therefore evident that if the surgeon is convinced by the adequacy of the investigations that a patient's symptoms are due to hyperinsulinism, he should be prepared to perform a subtotal pancreatic resection even in the presence of an apparently normal pancreas.

As, normally, islet tissue is found in the greatest quantity in the tail and body of the pancreas, it would not be surprising if multicentric tumour development resulted in the adenomata being concentrated in these areas. Serial sections of the excised portion in the present case supported this view, and showed a diminishing number of tumours as the head was approached. This is, of course, of practical importance, as excision of the whole of the tail and the body will give the best chance of eradicating completely the tumour tissue. The process is simplified and its completeness ensured by removing the spleen at the same time. Despite these facts, the presence of some adenomata in the sections nearest the head makes it probable that there are further tumours in the head itself. The prognosis is therefore uncertain and further resection may be required.

Another lesson to be learnt from this case is that focal neurological disturbances may result from hypoglycaemia. This was shown by focal pareses in the early history, focal twitchings in the later fits, and predominantly unilateral E.E.G. abnormality, corresponding to these manifestations. Black *et al.* (1954) reported a case developing a hemiplegia, and it seems that vascular insufficiency may be superimposed on the more diffuse pathological changes of hypoglycaemia described by Lawrence *et al.* (1952), and resembling the findings in cerebral anoxia.

In obscure cases of epilepsy of late onset when investigations have failed to reveal a cerebral neoplasm, the diagnosis of cortical atrophy or cerebral arteriosclerosis is sometimes too easily accepted. Even if the fits are of focal type the possibility of hyperinsulinism should always be explored. A single normal early morning blood sugar should not, however, be considered to exclude the diagnosis, and complete starvation for at least twelve hours may be essential to produce the characteristic clinical picture and abnormally low blood sugars.

Summary

A case is described in which many of the well-known clinical features of hyperinsulinism were associated with unusual focal neurological manifestations.

The characteristic clinical, biochemical, and electroencephalographic abnormalities could be induced at will, but required very long preliminary starvation.

Subtotal resection of an apparently entirely normal pancreas revealed the very rare condition of adenomatosis of the islets of Langerhans.

This patient was originally referred to one of us (E. R. B.) by Mr. J. M. Small. We wish to thank Mr. S. G. Smith, of the Biochemistry Department at Dudley Road Hospital, for carrying out the blood-sugar estimations, and Dr. W. Whitelaw, Director of Pathology, Dudley Road Hospital, for his advice and encouragement.

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SYSTEMIC EMBOLISM AND LEFT AURICULAR THROMBOSIS IN RELATION TO MITRAL VALVOTOMY

BY

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The vast literature on systemic embolism in rheumatic heart disease was largely compiled before the introduction of surgery in the treatment of mitral valve disease. Some of the recent papers, such as those of Jordan, Scheifley, and Edwards (1951), and of Wallach, Lukash, and Angrist (1953), were based on necropsy findings and must have included a number of cases which would have been too advanced or too complicated for surgery.

The incidence of embolism and auricular thrombosis may well be different in the fatal and in the operable cases. Apart from Wood (1954), few authors have referred in any detail to embolism in the latter group. We have therefore reviewed our cases in order to ascertain: (1) the clinical features of patients with systemic embolism before operation; (2) whether it is possible to diagnose left auricular thrombosis before operation; (3) the significance of previous embolism and of left auricular clot in relation to operative and post-operative embolism; (4) the influence of valvotomy on the incidence of late embolism.

From a series of 430 patients on whom mitral valvotomy was performed, we have studied 118 who fall into one or more of the following three groups (Table I): (*a*) those with systemic embolism before operation; (*b*) those with left auricular thrombi found at operation; (*c*) those developing systemic embolism during or after valvotomy.

The surgeons concerned were Mr. T. Holmes Sellors, at the Middlesex, London Chest, and Harefield Hospitals; Mr. K. S. Mullard, at Harefield Hospital;

and Mr. E. F. Chin, at Southampton Chest Hospital. Seventy-one of the patients were operated on by one of us (J. R. B.) at the London Chest and Middlesex Hospitals.

TABLE I.—*Systemic Embolism and Left Auricular Thrombosis: Composition of Series*

	Middlesex	London Chest	Harefield	Southampton Chest	Total
Total cases ..	181	67	92	90	430
Embolism: Pre-operative	16	12	21	5	54 (13%)
Operative and post-operative ..	14	3	4	3	24 (6%)
Left auricular thrombi ..	25	16	18	9	68 (16%)

The selection of cases and technique of mitral valvotomy followed the usually accepted principles (Baker, Brock, Campbell, and Wood, 1952; Sellors, Bedford, and Somerville, 1953). The diagnosis of pre-operative embolism was based on the clinical history. With a few exceptions, the operative or post-operative emboli were observed in hospital.

Clinical Features of Cases Developing Systemic Embolism Before Mitral Valvotomy

Study was made of 54 patients, in whom 75 separate embolisms occurred. Of these patients 19 (35%) suffered two or more embolic accidents. The sites were: brain, 59%, with equal numbers on each side; right leg, 13%, and left leg, 11%; aorta, 7%; right arm, 4%; and other sites (kidney, spleen, mesentery), 7%. Pulmonary embolism occurred in 10 of these cases, but have not been included in this study.

The clinical findings were compared in the 54 cases with embolism and 200 successive cases of mitral valvotomy without embolism, to find out whether they had any distinguishing features.

TABLE II.—*Systemic Embolism Before Mitral Valvotomy: Sex and Age Incidence*

Group (%)	Sex		Age			
	Male	Female	20–29	30–39	40–49	50–59
Embolic	31	69	5	28	54	13
Control	16	84	18	44	30	8

TABLE III.—*Systemic Embolism Before Mitral Valvotomy: Incidence of Certain Symptoms and Signs*

Group (%)	Rhythm		Dyspnoea*		Orthopnoea	Paroxys. Dyspnoea	Mitral Incomp.	R.V. Enlarg. in E.C.G.		Heart Size (C.T.R.)			
	Reg.	A.F.	Grades 1–2	Grades 3–4				No	Yes	<50–54	55–59	60–64	65–69
Embolic	22	78	65	35	28	19	41	68	32	55	25	5	15
Control	61	39	58	42	45	41	25	70	30	58	20	13	9

* Dyspnoea, grades 1–4, correspond respectively to "mild," "moderate," "severe," and "extreme."

Tables II and III show that the patients with embolism differed from the control group in five main respects: (i) the ratio of men to women was 1:2.2, compared with 1.5; (ii) the average age was slightly higher; (iii) auricular fibrillation was present in 78%, as against 39%; (iv) dyspnoea was less severe, and orthopnoea and paroxysmal cardiac dyspnoea were less commonly encountered; (v) higher incidence of mitral incompetence (significant mitral systolic murmur and/or regurgitant jet at operation). There was no difference in the incidence of right ventricular enlargement as shown on the electrocardiogram, or in the heart size. The duration of auricular fibrillation was known with reasonable certainty in 24 patients whose rhythm was irregular when the embolism occurred. It ranged from a few weeks to over 12 years (two weeks to six months, 7 cases; one to three years, 9 cases; four to six years, 5 cases; over ten years, 3 cases). These figures show no remarkable difference from the data for cases without embolism. Multiple attacks of rheumatic fever or of rheumatic fever and chorea, with the associated liability to endocardial damage, had no influence on the incidence of embolism. In fact, embolism occurred in only one of 11 patients who had had two or more attacks of rheumatic fever, and in one of 10 patients with a history of both rheumatic fever and chorea.

Factors which might influence the rate of blood flow in the heart, such as congestive failure, the degree of mitral stenosis, and the size of the left auricular appendage, were reviewed (Table IV). Figures for the size of the left auricle proper are not included, because there was no difference between the two groups. Three patients with "giant" left auricles were operated upon; there was no history of embolism in any of them. Values for cardiac output were not available for the majority of the cases with embolism, because cardiac catheterization was considered inadvisable. However, a low output can be inferred from a mitral facies (Wood, 1954), and from a small pulse. The presence or absence of these signs was recorded in all cases.

TABLE IV.—*Systemic Embolism: Incidence of Certain Signs*

Group %	Congestive Failure	Size of L. Auric. Appendage			Mitral Facies	Pulsus Parvus	Degree of Mitral Stenosis	
		Large	Mod. or Normal	Small			Severe or Mod.	Slight
Embolic..	22	51	41	9	16	29	76	24
Whole ..	17	28	40	32	27	31	86	14

Table IV shows that a history of congestive failure and a somewhat larger left auricular appendage were commoner in the patients with embolism. There was little difference in the severity of the stenosis as judged by the size of the mitral opening or by the presence of a pulsus parvus. The mitral facies was less often found in the embolic group.

These findings may be summarized as follows. In the group of patients with embolism prior to operation compared with 200 successive cases of mitral valvotomy without embolism, the sex incidence was less dominantly female; the age at operation was somewhat higher; auricular fibrillation was more common than sinus rhythm; dyspnoea was less severe; orthopnoea and paroxysmal dyspnoea were less frequently encountered; the incidence of mitral incompetence was slightly greater; and the left auricular appendage was larger. More than one-third of the patients developed a second or a third embolism.

Operative and Post-operative Embolism

Systemic embolism was closely related to mitral valvotomy in 24 patients (6% of 430 valvotomies), occurring during operation in 17, within a few hours in 2 and within fifteen days in 5. There were 4 late emboli—after seven weeks, one year (2 cases), and sixteen months. The sites involved were: brain, 17; aortic bifurcation, 4; left arm, 4; left leg, 2; and right leg, 1. Four patients sustained two emboli, making a total of 28 separate embolic incidents. There were 7 fatalities—5 from cerebral embolism during or within a few days of operation. The sixth death followed a cerebral embolism one year after an apparently successful valvotomy. Saddle embolus of the aorta developing during operation accounted for the seventh; immediate embolectomy was performed, but gangrene of the legs necessitated bilateral amputation, and the patient died nine weeks after valvotomy. Of the 24 patients in this category, 5 (21%) had a history of pre-operative embolism.

A few features distinguished these patients from 200 others without embolism who underwent valvotomy. The ratio of males to females was 1:1.4, compared with 1:5; a large heart (cardio-thoracic ratio, 60% or greater) was found in 58%, as against 22% of the controls; clot was present in the left auricular appendage in 64% of the patients with emboli, but in only 16% of the whole series;

and the mitral valve was calcified in 50%, compared with 35% in the control series. A large left auricular appendage was present as often in the group with emboli (29%) as in the controls (28%), and the incidence of mitral incompetence was of the same order in both groups (31% and 25% respectively). Other features such as the degree of dyspnoea, the electrocardiogram, congestive failure and the size of the left auricle were similar in both groups.

Relation of Operative and Post-operative Embolism to Pre-operative Embolism and Left Auricular Thrombosis

Five of the 54 patients (9%) with pre-operative emboli suffered a further embolic incident at or after valvotomy. This compares with an incidence of 6% in 376 patients without an embolic history who underwent valvotomy.

At operation 68 patients had a thrombus in the left auricular appendage; 11 (16%) of them developed an embolism during or after operation. The relationship between thrombus in the left auricular appendage and operative embolism is better shown by the higher incidence of thrombus (64%) in the embolic group than in the controls (16%). From the limited figures available, it is impossible to state the magnitude of the extra risk involved in operating on a patient with a history of embolism. However, it would not appear to be sufficient to justify withholding valvotomy, especially in view of the beneficial effect on the incidence of repeated embolism, referred to below.

Influence of Valvotomy on Late Embolism

The successful results following valvotomy soon raised the possibility that recurrent embolism complicating mitral stenosis might itself be an indication for surgery. Removal or lessening of the obstruction at the mitral valve seemed likely to reduce the chances of auricular thrombosis by increasing blood flow and by preventing stagnation in the auricular appendage. Four patients have developed late emboli—after seven weeks, one year, (2 cases), and sixteen months. One of these had two embolisms before operation. Thus in a follow-up period ranging from a few months to four years, the incidence of embolism after valvotomy has been less than 1%.

Pre-operative Diagnosis of Left Auricular Thrombosis

Clot was found in the left auricle or its appendage in 68 (16%) of the 430 cases of mitral valvotomy. It was more than twice as common (30%) in those with a history of previous embolism as in those without such a history (13%). The ratio of males to females was 1:2.3, compared with 1:5 in the control series; auricular fibrillation was present in all cases; and mitral calcification was found in over half the cases (53%), compared with 35% in the controls. Calcification was equally common in those above and those below 40 years of age. The average size of the heart and of the auricular appendage was similar in both groups, but in a quarter of those with thrombi the appendage was shrivelled and its lumen obliterated. Other features reviewed were equally unrewarding in pointing to any distinguishing clinical pattern of cases with left auricular thrombosis.

Pathology of Auricular Thrombosis

When a thrombus forms in the auricle or in its appendage, organization starts as soon as it becomes adherent to the living endothelium. The clot is invaded by capillaries, and fibrosis and, later, myxomatous degeneration may occur. The lumen of the appendage becomes obliterated and finally disappears, the appendage itself shrivelling up.

The organizing thrombus is rapidly covered with endothelium. One this process is complete, the risk of further thrombosis on the surface of the original thrombus is considerably reduced. Similarly, once the organization is well established, there is very little chance that the "grey" thrombus so formed will become detached, for emboli almost always consist of "red" thrombus which has become dislodged before organization has had time to start.

The majority of organized thrombi found in the left auricle have been wholly or partially in the appendage. Bailey *et al.* (1952) state that all thrombi arise in the appendage. Jordan *et al.* (1951), however, noted that less than half of the auricular thrombi found post-mortem were confined to the appendage, and in 16% of their cases the clots were localized in the auricle proper. Once a thrombus has formed, its tendency to remain in the appendage and to become organized there is explained by the presence of the columnae carneae which tend to entangle the clot as they traverse the lumen of the organ.

Jordan and his associates have stressed that thrombi eventually form in both the left and the right appendages in the majority of patients with long-standing mitral stenosis. Bull (1922) and Graef and others (1937) have stated that in their series the emboli arose from the thrombi in the auricle. However, it is more likely, in the light of the above description, that the presence of clots in the auricle merely indicates a tendency towards thrombosis at that site; those clots which adhere to the endothelium becoming organized *in situ*, whereas those which do not become fixed are carried into the systemic circulation as emboli. This suggestion is borne out by the clinical similarity between those patients who have had systemic emboli before operation and those who were found to have auricular thrombi.

The presence of organized clot in the appendage predisposed to the formation of further fresh clot there, and so increased the risk of post-operative emboli. "Red" clot was found alone in 6% of the cases in whom the type of clot was reported in detail, whereas it was present in 23% of those in whom there was already organized thrombus in the auricular appendage.

From the above description, once organization of a fresh "red" thrombus has occurred and a "grey" thrombus has been formed, there should be little risk of its dislodgment in the form of embolus. It should therefore follow that the risk of embolism at operation should be no greater when organized clot is present on its own than when it is absent. In this series, when "grey" clot was found in the auricle the incidence of systemic embolism complicating valvotomy was 10%; this figure is comparable with the 6% risk of this complication when no clot was found.

Where "red" clot was present, whether on its own or in combination with "grey" clot, the rate of embolism might be expected to be higher. In fact, systemic emboli were dislodged in 25% in this group. On the occasions when it was possible to determine the type of clot responsible for the embolus it was always the "red" variety.

A history of embolism prior to operation in no way makes it inevitable that clot will be encountered when the appendage is explored, for, although it may have formed there, the clot may have become dislodged in the form of an embolus before it had time to become organized and innocuous. In this series the appendage was found to be quite free from clot in 70% of cases with a history of embolism.

The finding of Jordan *et al.* (1951) of cases where the thrombus was confined to the auricle may account for some of the 10 post-operative emboli in our series where no auricular clot was found. In only one of our cases was thrombus described as being confined to the auricle proper, but this may be explained by the fact that the smooth surface of the thrombus is indistinguishable on palpation from the auricular wall.

A second cause of embolism from an apparently empty auricle is the dislodgment of pieces of calcium from the surface of the valve (Bolton, Maniglia, and Massey, 1952). This accident was thought to be responsible for four of the operative emboli in this series.

Technical Problems

The normal approach to the mitral valve through the auricular appendage may be impossible when the appendage either is filled by organized clot or has become so fibrosed and shrunken that even the little finger cannot be insinuated through its lumen.

Various methods have been described by which the mitral valve may be reached when the usual route is impassable. Harken did his earliest valvotomies through the superior pulmonary vein (Harken *et al.*, 1948). Although this approach is feasible, it has three disadvantages: the lumen of the vein may be too small to admit the finger; there is a risk that the vein may become occluded after it has been sutured; and it may be impossible to reach the valve with the finger if the auricle is unduly large.

In 1953, Temple described a method whereby an opening is made directly into the auricle at the bases of the pulmonary veins, where it may be "tented" and clamped. An incision is made into the muscular wall and the veins are separately controlled by tapes. This method avoids some of the disadvantages of the previous technique.

The approach via the auricular wall itself is undoubtedly the best. A purse-string suture is inserted into the auricular wall and haemorrhage is controlled by means of a Rumel tourniquet. The cavity can then be entered and re-entered with ease and with very little blood loss.

The method used at the Middlesex and London Chest Hospitals is as follows. The thrombosed appendage is palpated to determine whether the isthmus between it and the auricle is large enough to admit the index finger. If an approach via the appendage is thought possible, it is opened without the previous application of a clamp in the hope that any loose "red" clot may be washed out. (Clot has been removed in this way on 10 occasions.) The "grey" clot is dissected off the appendicular wall and the valve is approached in the usual way.

When the approach through the appendage is not possible, the lumen of the auricle is usually reached through the auricular wall direct, although the superior pulmonary vein has been used on three occasions and the base of the veins twice. Despite the fact that the finger had to be forced through the thrombus on several occasions, emboli were dislodged in only one of 10 patients in whom these methods were used.

The second technical problem is the prevention of systemic embolism at the time of operation, and the mitigation of its effects should it occur.

The risk of embolism during valvotomy is considerable; it was closely related to operation in 21 patients in this series (5%) and in 10% of the cases analysed by Wood. The embolus may lodge in either the cerebral or the peripheral vessels.

The mortality from cerebral embolism during valvotomy is high (45% in the present series and 66% according to Bailey), and in consequence various methods have been described to divert the clot from the cerebral vessels into those where its effects would be less disastrous. Carotid compression was advocated by Brock (Baker *et al.*, 1950) and others; this does not give protection to the vertebral arteries, but does lead to a temporary standstill in the column of blood between the point of compression and the aorta, and so emboli tend to be swept into the peripheral circulation.

Bailey *et al.* (1952) have described a method in which a clamp is applied to the innominate artery and a tape around the left common carotid is pulled tight during intracardiac manipulations. This technique has diminished the incidence of cerebral embolism, although it is not clear whether peripheral embolism has increased. It may be that emboli which would cause grave cerebral symptoms would be small enough to pass unnoticed when they lodged in peripheral vessels.

It has been suggested that the clamp used to control the haemorrhage from the appendage may crush a "red" thrombus which is projecting into the auricle, and that therefore the appendage should be opened before the clamp is applied. In this way, any loose thrombi will be swept out of the auricle.

In this series the method of carotid compression has been used particularly where there has been auricular fibrillation, where calcification has been present, and where clot has been felt in the appendage before it has opened. Although cerebral emboli have occurred despite this, the complication has been uncommon enough to justify the continuance of its use.

The third technical problem is concerned with the prevention of late emboli. Prior to the general acceptance of mitral valvotomy, it was proposed by Madden (1949) that the auricular appendage should be ligated or amputated in patients who were having repeated emboli. It was postulated that all emboli arose in the appendage and that therefore its removal would prevent the discharge of any more. More recently Bailey has recommended that the appendage should be removed in all cases after valvotomy, as he is of the opinion that if this is not done the cul-de-sac left behind is a potential source of danger. Although we have found that the size of the appendage bears little relation to the risk of post-operative embolism, whether early or late, it has latterly been our practice to amputate the organ when it has been at all large.

Summary

From a series of 430 mitral valvotomies, 118 cases have been studied to investigate the significance of systemic embolism and left auricular thrombosis in relation to mitral valvotomy.

There was a history of embolism in 54 patients (13%). Compared with 200 successive cases of valvotomy without embolism, these patients showed certain trends: the average age at operation was higher, the sex incidence was less dominantly female, auricular fibrillation was more common than sinus rhythm, dyspnoea was less severe, the left auricular appendage was larger, and the incidence of mitral incompetence was slightly greater.

Embolism was closely related to valvotomy in 6% of the 430 cases. When a previous embolism had occurred the incidence was 9%, and when left auricular thrombosis was present, 16%.

Left auricular thrombosis could not be diagnosed before operation. In general, it was found more often in males with auricular fibrillation and mitral calcification. It was more than twice as common (30%) in patients with a history of previous embolism as in those without such a history (13%), and was present in almost two-thirds of those who developed an embolus at operation. Embolism was encountered more than twice as often when "red" thrombus was found as when "grey" thrombus alone was present.

A successful valvotomy will not prevent further systemic embolism, but there is reason to believe it will reduce its incidence.

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CLINICAL TRIAL OF P.A.S. SALT OF ISONIAZID IN TREATMENT OF PULMONARY TUBERCULOSIS

BY

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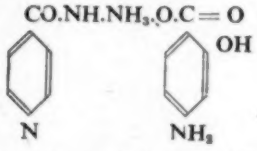
In 1953 Smith and Wiederkehr reported on the bacteriostatic properties against *M. tuberculosis* of a new drug then called GEWO 339. This is an additive compound between P.A.S. and isoniazid to which the following formula is attributed:



This substance was said to inhibit the growth of ordinary strains of tubercle bacilli at a concentration of 0.1 μg. per ml. of medium. It was also claimed that strains which were resistant to isoniazid and P.A.S., either alone or in combination, though not as sensitive as normal strains to GEWO 339, were nevertheless still sensitive at therapeutic levels. Strains which grew normally on media containing 100 μg. of isoniazid and also media containing 100 μg. of P.A.S. were inhibited by 5 μg. per ml. of GEWO 339. Brodhage, of the Institute of Bacteriology, Lucerne, confirmed these results in a personal communication.

The Investigation

In 1954 GEWO 339 became available in this country, and an opportunity presented itself to confirm the results of Smith and Wiederkehr and of Brodhage. For the sake of brevity the P.A.S. salt of isoniazid is referred to as the salt (Sa).

The technique of measuring the resistance of a number of strains of *M. tuberculosis* to Sa, P.A.S., isoniazid, and streptomycin used in this experiment is the standard technique described by the Medical Research Council (1953).

Fourteen strains were compared with the standard strain H37Rv. Of these strains, 10 were freshly isolated, but the remaining four were known to be resistant to either P.A.S. or isoniazid, or both. Of the remaining four strains, Nos. 8687 and 5300 were resistant to P.A.S. but sensitive to streptomycin, isoniazid, and Sa. Strain 9488 was fully sensitive to streptomycin, resistant to isoniazid and P.A.S., and, though still sensitive to Sa, was less sensitive than a normal strain, as slight growth occurred in a concentration of 1 μg. per ml. of Sa. Strain 9371 was fully resistant to isoniazid and P.A.S., showed a slight loss of sensitivity to streptomycin, and a similar loss of sensitivity to Sa, as once again slight growth occurred in a concentration of 1 μg. but not in 4 μg. The results are set out in Table I.

These results were thought to be sufficiently encouraging to justify a clinical trial of Sa. On ethical grounds it was considered undesirable to treat new patients with Sa. As it seemed likely that the drug would prove of value in patients infected with strains which were already resistant to streptomycin, isoniazid, and P.A.S., the following criteria for selection of patients for the trial were laid down. The patients should (1) have chronic pulmonary tuberculosis with one or more cavities and sputum strongly positive on two direct examinations within the last month; (2) be unsuitable for any treatment other than antibacterial drugs; (3) have had at least three months' treatment with isoniazid or P.A.S., either alone or together at some time in the past; (4) have had no change in treatment during the preceding two months—that is, drugs not started, changed or stopped, not newly confined to bed or allowed to get up at home, not admitted to or discharged from hospital; and (5) be likely to remain under the present regime for at least three months. These criteria were designed to reduce the chances of changes in sputum being due to other factors than the Sa. Patients with plentiful sputum were regarded as more suitable than those with only a trace. Out-patients were included.

TABLE I.—*Minimum Concentration Which Inhibited Growth*

	Streptomycin	Isoniazid	P.A.S.	Sa
H37	0·06	0·06	0·06	0·06
8687	0·06	0·5	64	0·06
5300	0·25	0·25	64	0·25
9488	0·06	64	64	4
9371	4	64	64	4

In laying down these criteria it was appreciated that only very chronic and extensively diseased patients would be available. Therefore, judgment on clinical or radiological grounds would be impossible. It was hoped, however, that comparison between the pre-treatment and post-treatment strains in their sensitivity to P.A.S., isoniazid, and Sa would yield valuable information concerning the efficacy of Sa in the treatment of pulmonary tuberculosis.

Five chest centres co-operated in providing patients, and altogether a total of 25 patients were offered. Of these six were rejected on the ground that the amount of sputum was insufficient and could not always be obtained.

For the first three weeks of the trial the patients received no drug treatment. During this period two 24-hour specimens of sputum were submitted to the laboratory each week. At the end of the control period treatment was begun. Sa was given as tablets, each of which contained 100 mg. of active substance, and each patient received a daily dose of 600 mg., in three doses of 200 mg. This treatment continued for 12 weeks, and during the whole period two 24-hour specimens of sputum were submitted to the laboratory each week. All the patients included in the trial were suffering from bilateral chronic pulmonary tuberculosis. All showed cavitation, which was bilateral in the majority of cases. Unfortunately, one patient, a woman aged 60 with severe bilateral tuberculosis and a sedimentation rate of 80 mm. in one hour, died shortly after treatment began and has had to be excluded. In a second case, that of a woman aged 43 with a long history of gastric ulceration, the ulcer perforated and she was withdrawn from the trial shortly after treatment had begun. The remaining 17 cases completed the trial without any untoward incident.

Results

Each 24-hour specimen was concentrated and cultured on Löwenstein–Jensen medium for four weeks, after which the cultures were read. The growth in all cases was very heavy, and any patient whose sputum did not yield a confluent growth in the majority of pre-treatment specimens was excluded from the trial. Subsequently, when under treatment the positivity of the sputum diminished, the cultures were divided into the following groups: (1) confluent growth, where no individual colonies could be detected; (2) scanty growth, where there was less than a total of 10 colonies on a pair of slopes; (3) moderate growth, for all degrees of growth between scanty and confluent; (4) no growth.

Sensitivity tests were performed on two of the cultures from the control period, and at weekly intervals after treatment had begun. Each strain was inoculated on to slopes of Löwenstein–Jensen medium containing the following concentration of drugs: streptomycin, 3 μg. and 15 μg.; isoniazid, 0.2, 1, and 5 μg.; P.A.S., 2, 10, and 100 μg.; and Sa, 0.2, 1, 5, and 50 μg. Partial resistance was reported when growth occurred on 3 μg. of streptomycin, 1 μg. of isoniazid, 2 μg. of P.A.S., and 1 μg. of Sa. Strains growing on higher concentrations were recorded as resistant.

TABLE II.—*Results of Sensitivity Tests*

Case No.	Sex and Age	Previous Treatment (Total Dosage in G.)				Pre-treatment					Post-treatment				
						First 3 Cults.	Sensitivities				Last 3 Cults.	Sensitivities			
		St.	P.A.S.	Isoniazid	Duration Months		St.	P.A.S.	Isoniazid	Sa		St.	P.A.S.	Isoniazid	Sa
1	M 64	104	840	64	64	CCM	S	S	R	S	CMM	S	S	R	Pr
2	M 38	194	4,740	69	39	CCC	Pr	Pr	R	Pr	ScMM	R	Pr	R	Pr
3	M 42	+++	+++	+++	48	CCC	R	S	Pr	Pr	MMM	R	S	Pr	Pr
4	F 34	113	4,060	30	46	MCC	R	S	S	S	OScSc	R	S	Pr	S
5	F 20	40	3,200	54	72	MCC	R	S	R	S	MMM	Pr	S	R	S
6	M 49	136	10,020	42·6	48	MCM	S	S	R	S	MScM	R	Pr	Pr	S
7	M 51	224	2,800	28	21	CCC	R	S	S	S	ScMM	R	S	R	S
8	F 34	198	3,700	79	27	CCC	R	S	R	S	ScOSc	Pr	S	R	S
9	M 46	308	3,436	34·6	53	CCC	R	S	S	S	MMM	R	S	S	S
10	F 34	130	11,540	30·6	50	MCC	R	S	Pr	S	MMC	R	S	S	S
11	F 38	65	1,300	0	38	CCC	S	S	S	S	MMM	S	S	S	S
12	M 62	84	9,400	38	51	CCC	S	S	S	S	OOO	S	S	S	S
13	M 35	200+	3,000+	18	48	CCC	R	S	S	S	OOO	R	S	S	S
14	M 71	204	3,600	9	46	CCC	S	S	S	S	OOO	S	S	S	S
15	M 53	58	2,080	0	4	MCC	S	S	S	S	OOO	S	S	S	S
16	M 40	60	1,200	0	3	CMC	S	S	S	S	OOO	S	S	S	S
17	M 48	102	760	25·2	4	CMC	S	S	S	S	ScOO	S	S	S	S

Drugs: St.=Streptomycin. Sa=P.A.S. salt of isoniazid. +++=Total dosage not known in Case 3. *Cultures*: Cults.=Culture. C=Confluent growth. M=Moderate growth. Sc=Scanty growth. O=No growth. *Sensitivities*:—S=Fully sensitive. R=Fully resistant. Pr=Partially resistant.

Details of the results, together with the total amount of previous antibacterial treatment and its duration, are set out in Table II.

Resistance to Sa

In no case did full resistance to Sa develop. In Cases 1, 2, and 3 partial resistance to Sa did occur in the final sensitivity tests. In Case 1 the pre-treatment strains were fully resistant to isoniazid, but sensitive to the other drugs. At the end of treatment the strains were still sensitive to streptomycin and P.A.S., but resistant to isoniazid, and partially resistant to Sa. In this case alone was there no fall in the number of bacilli in the sputum at the end of treatment. In Cases 2 and 3 the pre-treatment strains were resistant or partially resistant to isoniazid, and partially resistant to streptomycin and to Sa. In Case 2 the strains were partially resistant to P.A.S., but in Case 3 they were sensitive. At the end of 12 weeks' treatment with Sa, sensitivities were unchanged, but there was a substantial fall in the number of bacilli excreted. Both these patients had received very large doses of P.A.S. and isoniazid during the previous three to four years.

Cases 4–10 all exhibited some degree of resistance to isoniazid at some time during the trial, and all had previously had very large doses of isoniazid and P.A.S. In none of these cases did resistance to Sa develop, and in all cases there was a marked fall in the positivity of the sputum.

Cases 11–17 never showed any resistance to P.A.S. or isoniazid in spite of the previous treatment, and resistance to Sa did not develop in any case. In six of the cases sputum conversion occurred, and in the seventh case there was a marked fall in the number of tubercle bacilli recovered from the sputum.

Drug Tolerance

Sa was well tolerated in all cases. It will be seen from Table II that most of the patients had previously taken large doses of P.A.S., isoniazid, and streptomycin. The great majority of patients expressed their appreciation of the ease with which Sa could be taken in comparison with the nausea they had associated with large doses of P.A.S.

Discussion

The most striking change following treatment with Sa is the remarkable lowering of the positivity of the sputum in a group of patients suffering from chronic bilateral pulmonary tuberculosis with cavitation. In Case 1 only was there no significant alteration in the character of the sputum. In Cases 2–11 there was a marked drop in both the volume and the bacillary content of the 24-hour samples. In Cases 12–17 sputum conversion occurred. Of the six cases which showed sputum conversion, three had had antibacterial treatment over a period of approximately four years prior to treatment with Sa. None of these patients had previously had sputum conversion. The remaining three, although chronic bilateral cases, had previously had antibacterial treatment for a period of two to four months only. The results in these three cases suggest that Sa might be a suitable form of treatment in fresh and early cases of pulmonary tuberculosis.

In only one of the 17 cases did partial resistance to Sa develop during treatment. Two other cases, both of which had previously had very large doses of P.A.S. and isoniazid over a period of three to four years, were found to have strains of tubercle bacilli partially resistant to Sa before treatment was begun. In both these cases, however, sputum cultures became constantly less positive. In the remaining 14 cases no resistance to Sa developed.

Conclusions

This was intended as a small pilot trial to determine, firstly, that Sa was active *in vivo*, and, secondly, if drug resistance would develop quickly. Within the limits of a trial of this small size, the answer to both questions would appear to be favourable. It is hoped, therefore, on the basis of these results, to organize a larger full-scale trial of Sa. This paper is published in the hope that others actively engaged in the treatment of pulmonary tuberculosis will be encouraged to do likewise.

The cases in this trial were under the care of the following physicians at the various chest clinics and hospitals enumerated, and I would like to express my deepest thanks for their kind co-operation: Dr. J. R. Bignall, Chelsea Tuberculosis Dispensary; Dr. M. Caplin, tuberculosis officer, London Chest Hospital; Dr. Philip Ellman, East Ham Chest Clinic and Plaistow Hospital Chest Unit; Dr. L. J. Grant, St. Stephen's Hospital, Fulham; and Dr. Joseph Smart, London Chest Hospital. My thanks are also due to Messrs. Bengué and Co. Ltd. for providing the "dipasic" tablets, the P.A.S. salt of isoniazid used. I wish to express my gratitude to Miss A. M. Willings for her invaluable assistance in carrying out the laboratory side of this clinical trial.

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"The specialist in abnormal psychology is not the person who is, generally speaking, best qualified to teach preventive mental health principles. The ability to grasp the implications beyond the purely technical problem is not obtained by specific knowledge of psychopathology as such, but by an understanding of normal psychological development, by the ways in which human relationships develop and in which they are expressed and realized in normal society."—*Chron. Wld Hlth Org.*, 1955, **9**, 252.

CHANGES IN BODY WEIGHT ASSOCIATED WITH AGE AND MARITAL STATUS

BY

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Although it has long been recognized that changes in body weight are characteristic of certain diseases, surprisingly little is known about the sources of variation in weight of healthy people. There is no doubt that weight is related to height and that it increases with age even after adult stature has been reached. There is some evidence of small variations in association with region, season, occupation, and social class (Morant, 1948; Martin, 1949; Kemsley, 1950; Roberts, 1953; Clements and Pickett, 1954). It is also known that the weight added during pregnancy is considerably in excess of that due to the products of conception, and it is generally believed that women who have borne children are heavier on the average than those who have not. And there our knowledge appears to end.

This paper is based on data recorded during the pre-employment medical examination of industrial workers at two large firms in Birmingham. It examines the relation between marital status, child-bearing, and weight in women, and between age and weight in both the sexes.

Material

Cadbury Brothers Ltd., Bournville, and the General Electric Company Ltd., Witton, together employ about 16,000 workers. The data examined below were extracted from medical record cards at these two firms. The inquiry relates to 1,684 men and 5,081 women who had entered the firms within the last ten years and were in the age group 20–59 inclusive at the time of their pre-employment examination. The information available included weight, height, sex, age, marital status, and, in the case of married women, size of family. The workers were wearing indoor clothes and boots or shoes when they were weighed and measured; the size of family recorded referred to the number of children alive at the time of the interview.

Weight and Age

The mean weight of the women increased fairly regularly by about 3 lb. (1.4 kg.) for every five years of age, from 123.8 lb. (56.1 kg.) in the age group 20–24 to 139 lb. (63 kg.) at 45–49, an increase of a little over 15 lb. (6.8 kg.) in 25 years (Table I and Fig. 1). At higher ages there was no further increase; in fact, the data suggest that at ages above 50 the mean weight of women may decrease slightly. These findings are in close agreement with other inquiries into the relation between weight and age in women, and in particular with two previous examinations of weight of women factory-workers in this country. The first, a report of the Industrial Fatigue Research Board (Cathcart *et al.*, 1927), related to 3,000 women factory-workers, actively employed, who were weighed and measured in 1926. The second, an inquiry carried out by the Ministry of Food (Kemsley, 1950), was concerned with 33,500 women who were weighed and measured in 1943. The Birmingham data confirm that in women there is no middle-aged spread, but a steady increase in weight throughout the whole of reproductive life.

TABLE I.—*Mean Weight (lb.) Related to Age*

	Age (Years)							
	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59
Men ..	148·4 (396)	149·4 (381)	150·1 (246)	150·0 (170)	148·5 (153)	148·1 (147)	149·4 (109)	148·0 (82)
Women	123·8 (1,436)	127·1 (1,028)	129·8 (839)	132·7 (716)	136·4 (581)	139·0 (271)	139·0 (161)	135·9 (49)

In marked contrast to the regular increase in weight with age shown by the women, the mean weight of the men in this series varied very little with age (Table I and Fig. 1).

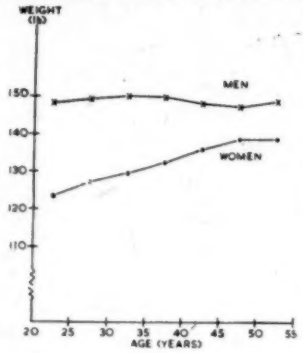

FIG. 1

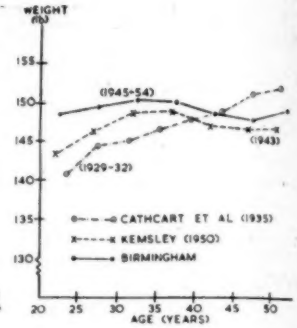

FIG. 2

FIG. 1.—Weight of men and women related to age. In Figs. 2, 3, and 4 the age plotted is the mid-point of the age group to which the mean weight or height relates. FIG. 2.—Weight of men related to age.

Indeed, none of the five-yearly age groups from 20–24 to 45–49 inclusive deviated by more than 1 lb. (0.45 kg.) from 149.1 lb. (67.6 kg.), the mean for the whole series.

This has not always been so. In 1884 Galton measured 7,000 men at his Anthropometric Laboratory in South Kensington; they showed a regular increase in weight with age comparable to weight–age curves for women (Ruger and Stoessiger, 1927). The same was true of the 10,000 men weighed and measured between 1929 and 1932 by Cathcart *et al.* (1935). However, using data on 27,500 men working in factories and in mines (collected by the Ministry of Food in 1943), Kemsley (1950) found that the pattern had changed. The weight–age curve for these men differed from earlier series in that, although there was a fairly regular increase in weight with age up to about 35 years, above that age it remained almost constant. In support of this observation Kemsley (1952) referred to figures for air-crew candidates given by Morant (1946), which agreed very closely with his own observations on male civilians, and showed that during the early years of the war there was little or no increase of weight with age beyond the age of 30.

Further confirmation of this wartime observation has recently been provided by Clements and Pickett (1954) in an analysis of data recorded by medical boards of the Ministry of Labour and National Service in Scotland between 1939 and 1946. They found a steady increase in weight with age up to 30 years, but little change above that age. When attention was restricted to men in social classes 1 and 2, however, at ages over 30 the mean weight increased with age in much the same way as in pre-war series.

It seems clear that in this country during the past 30 years the weight–age relationship for male factory workers has changed (Fig. 2). At the beginning of the century weight increased regularly with age for both males and females. This association has persisted for women, but for men it has gradually been eliminated. In the early years of the war it was still in evidence up to the age of 30 or 35 years. Since the war, however, if the present series is representative, the increase of weight with age for males has almost entirely disappeared and there is now little variation in mean body weight once adult stature has been reached.

At this point it must be emphasized that in each of the three series illustrated in Fig. 2 (and in all comparable

investigations reported in the literature) the data related to a cross-section of the working population at a given time, and not to a follow-up of the same men weighed at different ages. Hence men in the different age groups were samples of populations born at different periods. Since there has been a steady improvement in the standard of living during the past half-century, it is conceivable that the recent change in the weight–age pattern of cross-sections of the adult population may reflect the influence of socio-economic circumstances during childhood and adolescence upon adult stature rather than indicate that men no longer tend to put on weight with age. However, although it is true that children of wage-earners reach adult stature two to three years earlier than they did 70 years ago, there is no evidence that there has been any appreciable increase in their mean height at maturity over the same period (Clements and Pickett, 1952). Fig. 3 lends support to this view; it demonstrates that there was no substantial change in the negative association between height and age in the three series.

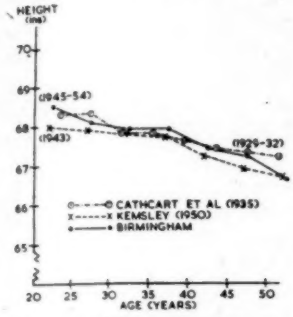

FIG. 3.—Height of men related to age.

It seems permissible to conclude that the tendency for male factory-workers to put on weight as they get older has disappeared during the past 20 to 30 years. On the other hand, the decline in height with age (Fig. 3) commonly observed in cross-sectional studies of the adult population is still present, and can be attributed mainly to a tendency for adults to decrease in height as they get older, rather than to the fact that the older members of the population had a less favourable childhood environment than the younger ones.

Weight and Marital Status

In each five-year age group married women were heavier than single women (Table II and Fig. 4), and the difference increased fairly regularly with age. Between the age groups 20–24 and 45–49 weight of married women increased by more than 16 lb. (7.3 kg.), while weight of single women increased by less than 6 lb. (2.7 kg.).

TABLE II.—*Mean Weight (lb.) Related to Age and Marital Status*

	Age (Years)							
	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59
Single men	148·4 (305)	150·1 (157)	146·3 (76)	152·7 (39)	149·2 (29)	145·1 (13)	145·9 (8)	143·1 (8)
Married men	148·6 (91)	148·9 (224)	151·8 (170)	149·2 (131)	148·3 (124)	148·4 (134)	149·7 (101)	148·5 (74)
Single women	123·6 (907)	125·6 (394)	125·4 (192)	128·4 (114)	130·5 (87)	129·4 (35)	134·5 (23)	132·4 (16)
Married women	124·2 (529)	128·1 (634)	131·0 (647)	133·4 (602)	137·4 (494)	140·6 (236)	139·7 (138)	138·0 (33)

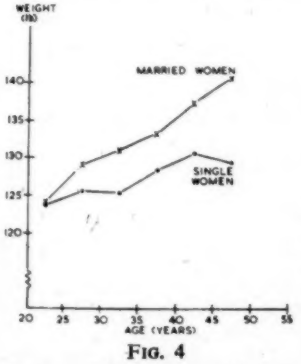

FIG. 4

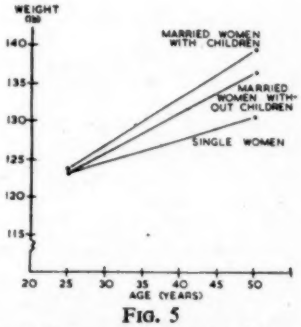

FIG. 5

FIG. 4.—Weight of married and single women related to age.
FIG. 5.—Weight of married women with children, married women without children, and single women related to age.

There was no very obvious difference between the weights of single and married men (Table II), and it seemed possible that the difference in the case of women would be due to the effect of child-bearing. It is true that at all ages women with children were heavier than those without children (Table III). The difference was not great, however, and at a given age weight did not increase very regularly with the number of children. Indeed, in the higher age groups women with small families were slightly heavier than those with large families.

Moreover, in each age group married women without children were heavier than single women; the difference increased with age and was considerably greater than the difference between married women without children and married women with children (Tables II and III). This observation is illustrated in Fig. 5, in which straight lines have been fitted to the data by the method of least squares. The equations for the regression of weight (y lb.) on age (x years) were as follows:

For single women	$y=0.30x+117.1$
For married women without children	$y=0.54x+112.3$
For married women with children ..	$y=0.63x+111.3$

The effect of child-bearing is evidently not the sole or even the most important reason for the difference in weight between single and married women. It is not difficult, of course, to suggest other factors that may play some part in promoting this weight difference. For example, it may be related in part to opportunity and incentive for preparing meals. It is also possible that the present-day fashion for slimness in women may have contributed to the observed difference. (Single women may make a more determined effort to control their weight by dieting.) Further, it is conceivable that in marriage regular intercourse may influence weight. The list of possible explanations could be extended, but in the absence of evidence it is sufficient to recognize that the association between weight and marital status in women is unlikely to be attributable to any single cause.

TABLE III.—*Mean Weight (lb.) of Married Women Related to Age and Size of Family*

Size of Family	Age (Years)						
	20–24	25–29	30–34	35–39	40–44	45–49	50–54
0	123·6 (387)	127·8 (313)	129·5 (178)	129·6 (122)	136·1 (73)	140·7 (39)	135·8 (31)
1	125·2 (133)	128·0 (213)	130·1 (244)	135·0 (175)	135·9 (172)	137·5 (67)	138·5 (29)
2	132·4 (9)	128·4 (94)	132·3 (158)	133·0 (184)	135·9 (137)	145·6 (65)	147·7 (32)
3	—	135·9 (15)	135·9 (66)	135·7 (121)	142·5 (111)	138·3 (65)	137·6 (46)

Summary

This inquiry relates to 1,684 men and 5,081 women in the age group 20–59 working in two large Birmingham firms. Data on weight, height, age, marital status, and, in the case of married women, size of family were extracted from medical record cards. The information had been recorded at the time of the pre-employment medical examination.

The mean weight of the women increased regularly by approximately 3 lb. (1.4 kg.) every five years (from 123.8 lb. (56.1 kg.) in the age group 20–24 to 139.0 lb. (63 kg.) at 45–49). The weight of the men showed very little variation with age. Comparison with earlier series suggested that an increase in weight with age exhibited by males at the beginning of the century has gradually disappeared.

In each five-yearly age group married women were heavier than single women. At corresponding ages married women with children were a little heavier than married women without children, but married women without children were considerably heavier than single women.

It is suggested that factors other than child-bearing play an important part in promoting the weight difference between married and single women.

We are greatly indebted to Messrs. Cadbury Brothers Ltd. and the General Electric Company Ltd. for permission to extract data from their medical record cards.

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THE BETA-LIPOPROTEIN AND CHOLESTEROL CONCENTRATIONS IN SERA OF NIGERIANS*

BY

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The relation of diet to the development of atherosclerosis can be studied in contrasting cultural groups which have different dietary habits. This appears to be one approach to a study of the late effects of diet upon this form of chronic disease.

In a previous study of Central American subjects (Mann, Munoz, and Scrimshaw, in press) we have demonstrated that there are striking differences in the serum lipid patterns among populations with different environmental characteristics. It was shown that the serum cholesterol levels of adults of either sex averaged less than 175 mg. per 100 ml. at all ages, that these levels were not significantly related to age, and that, while the rural Central Americans were thin as judged by relative weight $\left(\frac{\text{observed weight}}{\text{desirable weight}}\right)$, this thinness could not account for the low serum cholesterol levels observed. In contrast to these findings with cholesterol, the serum beta-lipoprotein levels of the rural Central Americans were similar to those of age- and sex-matched North Americans. There was thus a unique disparity between the lipid patterns of the largely vegetarian Central Americans and the North American comparison group. A comparison group of urban Guatemalans were similar in both dietary and serum lipid patterns to North Americans. These observations promise to illuminate the problem of the relative atherogenicity of the various serum lipid components. They require further study to determine the mechanisms which control these various serum lipid components.

The studies reported here were undertaken at about the same time to extend these observations to another racial group in an entirely different environment in order to verify the findings described, and to minimize the possibility that genetic factors might be responsible. The serum cholesterol and lipoprotein levels of 46 Nigerian men have been studied, and dietary and cultural evaluations have been made which permit segregation of these into three groups. The resulting data resemble those obtained in Central America, and confirm the belief that primitive peoples, consuming largely vegetarian diets, with a high calorie turnover in relation to body size, show low levels of serum cholesterol coupled with beta-lipoprotein levels similar to those of urban United States citizens.

Methods

Nature of the Sample

The Nigerian subjects were drawn from three different areas of the country. The cultural characteristics and dietary patterns differ considerably between these three areas. Group A consisted of natives of the dry northern part of Nigeria, coming from Moslem tribes whose staple foods are sorghum and millet (*Pennisetum* spp.), who eat little fish or meat, and whose diet contains little fat apart from that present in the vegetables consumed. Group B was composed of natives of the Ibo tribe from the humid Eastern Region, whose staples are yams (*Dioscorea* spp.) and cassava (*Manihot utilissima*), which they supplement with reasonable quantities of green and leafy vegetables, fruit, and a little fish or meat. Their diet contains red palm oil, but the total fat content is low compared with that of North Americans. Group C was drawn from pagan tribes of the Middle Belt of Nigeria, that area which lies along the banks of the rivers Niger and Benuë in their westward and eastward passage through the country. These people eat both roots and grain, a little fish, and red palm oil.

The wealthier members of these tribes were excluded from this investigation, and the three groups consisted of peasant farmers and the labouring classes. Such peasants, at all ages, expend large amounts of energy from their limited calorie resources to maintain themselves at a subsistence level, and, in contrast to that of North Americans, their weight decreases with age after the fourth decade (Nicol, 1952).

Apart from a clinical impression that the acute complications of atherosclerosis are rarely seen in these Nigerian peasants, little is known of the incidence of this disease from necropsy material studied in Nigeria. However, Edington (1954) has studied 3,645 reports of necropsies carried out in the Gold Coast, where the cultures are somewhat similar to those of Nigeria, and has recorded a low incidence of hypertension (0.2%), atheroma (0.5%), and coronary disease (0.8%).

Clinical Examinations

The subjects in all three groups were examined in Kaduna General Hospital while they were convalescent from minor surgical procedures. A general clinical examination was performed, heights, weights, and blood pressures were recorded, and individuals suffering from gross infestations or active disease were excluded. Signs of cardiovascular disease were not observed clinically, and in all but one individual, whose blood pressure was 140/90, the systolic and diastolic tensions were low.

Dietary Methods

The diets of the subjects forming the sample were not measured individually. When in hospital they ate food brought in for them by relatives living in Kaduna, this being the normal custom in Nigeria. Such is the conservativeness of these people regarding dietary patterns that their food intake, in whatever part of the country they happen

* A portion of this work was completed while Dr. G. V. Mann was an Established Investigator of the American Heart Association.

to be living in, differs little from that typical of their native tribe in its own environment. The characteristics of these typical tribal diets have been established by studies carried out over the past eight years, and are shown in Table I. The methods employed and the data obtained have been fully documented elsewhere (Nicol, 1949, 1952, 1953), and

TABLE I.—*Dietary Characteristics of Three Nigerian Tribes Studied*

Group:	A	B	C (Middle Belt)
Culture	Moslem	Ibo	Pagan
Staples	Sorghum, millet	Yam, cassava	Sorghum, yam
Alcohol	Very little	Palm wine	Sorghum beer, palm wine
Calories	2,800	2,350	2,500
Protein—animal	3 g.	20 g.	6 g.
„ plant	90 „	26 „	70 „
„ total	93 „	46 „	76 „
Fat	26 „	45 „	45 „
„ % of calories	8	15	15

confirmed in more recent studies as yet unpublished (Nicol). The nutrient composition of the diets was computed from Platt's (1945) "Tables of Representative Values of Foodstuffs commonly used in Tropical Countries," additional information being obtained from the United States Department of Agriculture's "Composition of Foods used in Far Eastern Countries" (Leung, Pecot, and Watt, 1952) and from the Food and Agriculture Organization's "Food Composition Tables for International Use" (Chatfield, 1949).

Biochemical Methods

All blood samples were taken in the early morning before the first meal, and the sera were separated the same day in the laboratories of the West African Institute for Trypanosomiasis Research. The sera were stored in a refrigerator overnight and dispatched by air the next day in a large flask of ice. The ice was replenished at Lagos and Accra (Gold Coast) when necessary. The sera reached the laboratories in Boston within five days of being separated, having been kept at 0–5° C. while in transit.

The analysis of beta-lipoproteins was done by the ultracentrifugal method of Gofman (Gofman *et al.*, 1950). The total cholesterol was measured by the method of Abell (Abell *et al.*, 1952).

Statistical Methods

The comparison of means of the three Nigerian subgroups was done by conventional "t" tests. For this purpose the subjects were not considered according to age. The comparison of the Nigerian subjects with North American data (Mann, Lawry, O'Connell, Wysocki, and Stare, in preparation) was done by a matched series method in which a Nigerian subject was randomly matched with one or more North American subjects according to age and relative weight. It was possible to match 30 of the Nigerian subjects by this procedure. While the data of 81 North American subjects were used to supply means of those who matched, these means were taken as contributing one estimate each, so that each comparison group contributed 29 degrees of freedom.

Results

A description of the cultural characteristics and diets of the Nigerian subjects is shown in Table I. Those diets are characterized by their low calorie content in relation to the physical activities required, the low level of animal protein in all groups, the low total protein level of Group B, and, finally, the low fat content of all the diets. The groups differ among themselves principally in the lower protein content of Group B.

The summaries of the serum lipid measurements of the Nigerian subjects are shown in Table II as means and standard deviations. When the differences of these were examined, only the difference of the S_f 12–20 level between Group A and B was found to exceed a probability of 5%, that the observed level of Group B exceeded that of Group A by more than would be expected from sampling error.

The similarity of the three subgroups in respect to age, relative weight, and diet, as well as serum lipid levels, seemed to justify their pooling for the matched series comparison with North American subjects, which is summarized in Table III. This comparison revealed a highly significant

TABLE III.—*A Comparison of the Serum Lipid Levels of 30 Nigerian Men with those of an Age- and Weight-matched Group of United States Men*

	S_f 12–20 (mg./100 ml.)		S_f 20–100 (mg./100 ml.)		Total Cholesterol (mg./100 ml.)	
	$\bar{x}$	±S.D.	$\bar{x}$	±S.D.	$\bar{x}$	±S.D.
Nigerian	25·4	±14·5	40·1	±29·8	129·9	±43·1
North American	33·6	±17·0	58·3	±45·5	212·6	±42·8
t	2·01		1·83		7·39	
Degrees of freedom	58		58		57	
P	0·05		>0·05		$>10^{-12}$	

difference of serum cholesterol levels. The Nigerian subjects showed levels averaging 83 mg. per 100 ml. lower than the North American comparison group. The S_f 12–20 levels of the North Americans were higher by an average of 9 mg. per 100 ml., and this difference had a probability of 0.05, but the observed S_f 20–100 difference was not significant ($P > 0.05$).

Discussion

These data confirm the observations previously made in Central American subjects. They indicate that some environmental factors are at work which prevent the rise of serum cholesterol levels with age which is characteristic of North Americans. The Nigerian subgroups did not appear to differ significantly among themselves.

There are at least three explanations for these phenomena which are suggested by the data. The differences of serum lipid patterns among the comparison groups might result from (*a*) differences of fat intake, (*b*) differences of physical activity, (*c*) differences of protein intake.

The differences of fat intake among the groups represent an attractive explanation, and one which has been exhaustively documented by Keys (1953) and Keys and Keys (1954). There are certain difficulties with this explanation. Why and how does the lower fat intake of the vegetarian groups selectively affect the serum cholesterol concentration without influencing the beta-lipoprotein levels? Why are dietary restrictions of fat in North American subjects not more effective in reducing the serum lipid levels (Keys, 1952), and why, when reduced to the low levels of the Central American and African groups studied here, are they

TABLE II.—*Serum Cholesterol and Beta-lipoprotein Concentrations of 46 Nigerian Men, Grouped According to Cultural Origins*

Group	Age (Years)		No. of Subjects	Relative Weight		S_f 12–20 (mg./100 ml.)		S_f 20–100 (mg./100 ml.)		Total Cholesterol (mg./100 ml.)	
	$\bar{x}$	±S.D.		$\bar{x}$	±S.D.	$\bar{x}$	±S.D.	$\bar{x}$	±S.D.	$\bar{x}$	±S.D.
A	28·8	±8·8	23	0·87	±0·09	21·1	±11·5	36·7	±26·9	118·8	±43·9
B	29·2	±11·9	14	0·91	±0·12	30·2*	±13·5	44·9	±35·2	129·9	±40·9
C	29·9	±13·2	9	0·91	±0·04	22·3	±11·0	43·8	±21·5	119·9	±33·7
Combined groups	29·1	±10·5	46	0·89	±0·10	24·1	±12·5	40·6	±28·5	122·5	±40·6

*$P < 0.05$ in AB comparison.

often found to increase the serum cholesterol levels (Hatch and Kendall, 1952)? We are inclined to doubt that the serum lipid differences observed in the present studies are caused by low fat intakes.

We have proposed in another study (Mann, Teel, Hayes, McNally, and Bruno, submitted for publication) that muscular exercise may exert an effect in reducing or controlling the serum lipid levels in a manner analogous to the favourable effect of exercise on carbohydrate tolerance in diabetic subjects. This hypothesis would attribute the low cholesterol levels found in Guatemalans and Africans not to the limited diet but to the muscular activity and energy expenditure required in those cultures. This proposes that a large muscle mass or a large muscular expenditure is the effective agent, and that this, not the diet, is the important element in preventing hyperlipaemia and perhaps atherosclerosis. Reflection will show that such an explanation is at least as compatible with the available observations as is the dietary fat explanation which has been so widely advocated. When this effect of exercise was examined experimentally in human subjects it was found that doubling the calorie intake of young men who were consuming a very high fat diet did not increase the serum cholesterol or lipoprotein levels so long as the excess energy was expended in physical activity. There was some evidence that physical training actually diminished the serum lipid levels in the presence of large food intakes, and that a large muscle mass tended to delay the hyperlipaemia which results from periods of positive calorie balance (Walker *et al.*, 1953). The same experiment did not confirm the hypothesis that the level of serum beta-lipoprotein is directly correlated with the magnitude of the energy exchange.

There is no evidence in human subjects that the protein intake influences the regulation of the serum lipid levels. We have shown in cebus monkeys (Mann *et al.*, 1953) that a mild deficiency of cysteine and its precursors is necessary for the production of hyperlipaemia and atherosclerosis in that species by cholesterol feeding. The association of *low* dietary protein intakes with *low* serum lipid levels, and the dissociation of cholesterol and beta-lipoprotein levels in the human subjects studied here, all detract from the possibility that these dietary situations produce the same results in the two species.

Summary

It has been shown that the serum cholesterol levels of 46 Nigerian men were significantly lower than the levels of an age- and weight-matched group of United States citizens. The serum lipoprotein levels of the Nigerians were only slightly lower than those of the North Americans, and these differences were of doubtful significance.

The Nigerian subjects were found to consume diets of low protein and fat content.

The relation of these dietary characteristics to the serum lipid findings has been discussed.

The data are interpreted as supporting a hypothesis which relates muscle mass and the magnitude of energy expenditure to the control of the serum lipid levels.

We are grateful to the Chief Medical Adviser to the Federation of Nigeria for permission to publish this paper.

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TRUE ENTEROLITHS OF THE SMALL INTESTINE

WITH REPORTS OF THREE CASES

BY

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True enteroliths of the small intestine are of three main types: (1) those consisting mainly of bile acids; (2) those consisting mainly of calcium oxalate; and (3) those consisting mainly of phosphate. Bile acid enteroliths are formed mainly of choleic acid; a small proportion of cholic acid may also be present. Two such stones, formed in duodenal diverticula, were analysed by me a few years ago (Fowweather, 1949), and the clinical features of the case were also described (Armitage, Fowweather, and Johnstone, 1950). Three cases involving the other types of stone have since come to my notice.

Case 1

The first case was that of a woman of 65 who was first seen by Dr. A. Leese, who diagnosed the presence of enteroliths and referred her to Mr. George Armitage for operation. It was then found that a portion of small intestine just proximal to the ileo-caecal valve was the seat of considerable changes. These consisted mainly of a series of constrictions, eight in all, with stones lying in pouches above some of the dilatations. To indicate the position of the stones the constrictions were numbered 1 to 8, from the ileo-caecal valve upwards.

Stones Marked "Above 8."—Two stones were present, both dark brown in colour and oval in shape. (1) Weight 10 g.; length 30 mm. In the centre was a plum stone weighing 0.6 g. The material surrounding it was dark in colour and laminated. There was evidence of loss of part of the outer layer. When broken, the fractured surface was lighter in colour than the unbroken surface, and when powdered was bright orange. (2) Weight 7 g.; length 28 mm. In the centre was a plum stone weighing 0.5 g. The surrounding material was very similar to that of (1) and also showed some loss from the outer layer.

Stones Marked "7 and 8"—Two stones were found between constrictions 7 and 8. (1) This was a plum stone weighing 1 g. and 22 mm. in length. The surface was shiny and smooth as if worn. (2) This was also a plum stone, covered with a thin, hard, yellow-brown coating. Total weight 1.4 g.; length 24 mm. The plum stone itself weighed 1 g.

Stone Marked "5 and 6."—This was of irregular shape (about 12 mm. in diameter) and weighed 0.8 g. It had the same brownish colour as those already mentioned, but no foreign body could be recognized within it. It is conceivable that a portion of the outer layer lost from the first or second stone referred to may have acted as the nucleus for deposition in this case.

Stone Marked "4 and 5."—This was a small plum stone, weight 0.5 g. and length 17 mm., covered with a thin shell of deposit which weighed 0.1 g.

Stone Marked "3 and 4."—This was 18 mm. in length and weighed 1 g. It was a small fruit stone, in shape and size more like a cherry stone than a plum stone, covered by a layer of deposit, from which portions had been lost. The fruit stone weighed 0.4 g.

Stone Marked "2 and 3."—This was 16 mm. long and weighed 1.1 g. It had a smooth, unbroken surface and was a small fruit stone weighing 0.3 g. and 15 mm. long, with a thin black-and-brown covering. It resembled a damson stone.

Analysis

"Above 8."—These stones were much the largest and provided the most suitable material. The coverings of the two fruit stones were identical in appearance, and were ground up together to a fine powder and used for the analysis. The results were :

Moisture (loss at 100° C.)	5.16%
Free fatty acids	0.27%
Neutral fat and cholesterol	0.15%
Bile acid (mainly choleic acid)	5.45%
Calcium oxalate	85.11%
Calcium sulphate	0.78%
Bile pigment, food residues, etc.	3.08%
	100.00%

Examination of the other materials showed a substantial amount of calcium oxalate—that is, they were qualitatively similar to the above, but there was evidence of some quantitative differences; there seemed little point in making detailed analyses of all of them even if the quantity of material available had made it possible. Some of the differences noted were :

"7 and 8."—The covering of (2) when ground was not so bright as "above 8."

"5 and 6."—This also differed in colour, being of a dark buff shade. This material contained less calcium oxalate and more bile acid than "above 8."

"4 and 5."—Similar in colour to "5 and 6" but harder, and contained more oxalate.

"3 and 4."—Darker in colour than any of the above, and harder; probably contained still more oxalate.

"2 and 3."—Very similar to "3 and 4"; if anything, a little darker in colour.

Case 2

The second case was that of a woman of 63, who was operated on by Mr. Digby Chamberlain. He found a loop of small intestine a short distance above the ileo-caecal valve. This loop had been formed many years earlier by a short-circuit operation which had been carried out to relieve an intestinal obstruction. Mr. Chamberlain removed the loop, and in it were four stones. All were similar in shape, size, and colour, being disk-like and roughly circular in outline, and almost black. I obtained two stones for analysis, the other two being retained with the excised loop of intestine for a museum specimen.

The first stone was about 25 mm. in diameter and weighed 3.2 g. It had a hard shell with a faecal core. The second was slightly larger and weighed 3.7 g.; its core was a plum stone 20 mm. in length. Both were laminated. A portion of the shell of the first stone was used for qualitative analysis, and the residue was later added to the shell of the second for quantitative analysis; moisture was first removed by drying in the steam oven. The analysis showed :

Free fatty acids	0.15%
Neutral fat and cholesterol	0.44%
Bile acid (mainly choleic acid)	11.48%
Calcium oxalate	83.45%
Bile pigment, food residue, etc.	4.48%
	100.00%

Case 3

This patient was a woman of 47 from whom Mr. Michael Oldfield removed a stone which he found impacted in the ileo-caecal valve. The stone was almost black in colour, of somewhat irregular shape, and weighed 2.5 g. Besides oxalate and phosphate it contained a considerable amount of organic matter. The analysis showed:

Neutral fat and cholesterol	2.47%
Bile acid (mainly choleic acid)	3.78%
Calcium phosphate	44.25%
Calcium oxalate	23.00%
Organic matter	24.30%
Undetermined	2.20%
	100.00%

It is hoped that more complete clinical details of these cases will be published later.

Stones in the Appendix.—In addition to the above, one case of stones in the appendix came to my notice. There were three stones—one about 13 mm. in diameter and two about 5 mm. in diameter, all dark brown. The stones contained a considerable amount of mineral matter, consisting mainly of calcium phosphate, together with organic matter in which protein and fat could be recognized. The composition seems similar to that of intestinal sand, but a more detailed analysis was not made.

Discussion

According to Blix (1935) a stricture or diverticulum of the small intestine is necessary for the formation of stones. Others have emphasized the importance which altered mechanical conditions must play in favouring the growth and retention of stones. Other factors are conditions favouring the deposition of some of the contents of the small intestine in insoluble form, and the presence of a suitable nucleus on which this material may be deposited and to which it adheres. It is possible that the body which forms the nucleus may sometimes play a major part in stone formation. The presence of plum stones in enteroliths has often been recorded in the literature, and it is tempting to regard them as more than a passive nucleus in some cases, for while smooth, rounded bodies may pass easily through the intestine, it seems likely that the sharp points of plum stones may well cause trauma, swelling, or spasm, which will result in slow passage of the stone or a definite arrest, giving ample opportunity for the deposition on them of insoluble material, so that they become true enteroliths.

The nature of the material forming the stones depends on conditions causing its precipitation, and this in many cases depends on the *p*H, which varies as one passes along the intestine. Hence each type of stone has a region where conditions are most favourable for its formation. But the locality in which a stone is found is not necessarily the place where it was formed; stones sometimes leave diverticula and pass further along the intestine, where they may gather other material before finally being removed. Also conditions where a stone is forming may favour the precipitation of more than one substance, so that, besides containing various proportions of food residues, they contain more than one substance that has been precipitated. Their rate of growth varies, owing to change in supply of the precipitated material or to change in *p*H where the stone is situated; these changes no doubt account for the fact that most stones consist of a number of layers.

Enteroliths consisting mainly of bile acid have been reported on about twelve previous occasions. All have been found in women, except in one case reported by Ward-McQuaid and Gordon (1950). In this case, that of a man of 80, multiple stones were found in a duodenal diverticulum. They were said to consist of cholic acid, but analytical figures are not given. It seems to me more probable that they consisted mainly of choleic acid. The conditions responsible for the formation of bile acid stones (of which an acid *p*H is one) have already been discussed by me in the report

already referred to. Their site of formation is usually the upper part of the small intestine.

According to McGee and Hastings (1942), the *p*H of the upper part of the small intestine is between 6.2 and 6.8 except in a few isolated instances. Information about the lower part appears to be less precise, but it seems to be accepted that the acidity decreases gradually as one passes further from the duodenum, so that the reaction in the lowest portion of the small intestine is frequently alkaline, and it is such a reaction which favours the precipitation of phosphate.

Stones of the small intestine consisting mainly of phosphate therefore have this part as their site of formation. Very few complete analyses of such stones have been recorded. More usually, the presence of phosphate is referred to in general terms. Thus Ho Dac Di (1935) removed from a woman of 40 a stone which he describes as the size of a mandarin orange, and which, on chemical analysis, revealed the presence of phosphate and oxalate of calcium; there were no calcium carbonate, cholesterol, bile pigments, or uric acid. More recently Richards (1951) removed three enteroliths from a woman of 44; he states that biochemical analysis indicated that they were composed mainly of organic debris, with some fat and lipoid matter and a moderate amount of calcium and magnesium phosphates.

Calcium oxalate may be precipitated at a slightly acid as well as an alkaline reaction, and may therefore be deposited in any part of the small intestine. Barth (1928) made what appears to be the first report of a small intestine stone consisting mainly of this substance; it contained over 78% of calcium oxalate and 20% of organic matter, the latter mostly faecal material; no mention is made of bile acids. Blix (1935) described an enterolith containing about 58% of calcium oxalate and 11% of choleic acid. Grettve (1947) discussed enteroliths at some length and described a case of his own. He referred to the above-mentioned cases of Barth and Blix as the only published cases in which the stones consisted predominantly of calcium oxalate, and considered it most likely that the oxalic acid required for the formation of these stones comes from the food, which in the bowel is combined with calcium. The stone in his own case was analysed and reported on by Blix (1947). It contained approximately 79% of choleic acid and about 3% of calcium oxalate. Blix at the same time reported on a small-intestine stone sent by Dr. Waldenström. The interior of this contained 56% of calcium oxalate and about 19% of choleic acid, while the surface layer contained about 70% of calcium oxalate and only very little bile acid.

It will be seen that, judging from published reports, cases of stones in the small intestine are rare. No doubt cases are dealt with from time to time without any report being made. Of some in the literature the composition is described only in general terms. It would no doubt increase our understanding of the subject, and probably of lithiasis in general, if all such stones were reported and analysed as completely as possible.

Summary

Two cases of enteroliths consisting mainly of calcium oxalate, and one whose main constituent was calcium phosphate, have been described, and an analysis of the stones in each case has been given. In addition, a case in which stones were found in the appendix has been briefly referred to.

The conditions and sites of formation of enteroliths have been briefly discussed.

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Medical Memoranda

A Case of Human Parasitization by Ixodes hexagonus, Leach (Hedgehog Tick)

A welder aged 45 had noticed, a week before seeking advice, what he took to be a wart on his neck, and covered it with a strip of adhesive plaster. By the sixth day the "wart" had grown much larger, and on removing the plaster to inspect it he was concerned to discover something moving between the "wart" and the skin.

The "wart" was bluish grey in colour, spindle-shaped, and $\frac{5}{8}$ in. (1.6 cm.) long by $\frac{3}{8}$ in. (1 cm.) at its widest part. Black legs could be seen moving between the "wart" and the skin. Gentle traction revealed that the "wart" was the abdomen of a tick engorged with blood. The front end of the parasite was so firmly embedded in its host that further traction caused a part of its abdomen to come away with the forceps, spilling about 1 ml. of blue blood. The colour of the "wart" was due to the colour of the ingested blood showing through the integument of the parasite's abdomen. Firmer traction dislodged it completely, leaving a reddened vesiculated area, which completely healed in two or three days. The patient had not felt the bite, nor discomfort at any time.

At the British Museum (Natural History Section) the tick was identified as an adult female of *Ixodes hexagonus*, a blood-sucking parasite. This tick is most commonly found infesting the hedgehog. Its life-cycle consists of four stages —those of egg, larva, nymph, and adult—the active stages requiring a feed of blood from a host before passing to the next stage. As at each feeding stage it drops from the host when fully fed, the tick has to find a fresh host after each moult. Apart from hedgehogs, the tick is found on stoats, weasels, ferrets, dogs, cats, and other mammals; and, very infrequently, on man.

Records kept by the Natural History Section of the British Museum show that hedgehog ticks brought for identification after being found on human beings—mostly on the head and neck—numbered about 20 between 1940 and 1951. Other specimens were found in garden shelters, houses, and factories. Because of the protection afforded by the adhesive dressing in this case the tick had been allowed to feed for so long on a human host. The relatively large number of cases of human infestation in 1944 (13) were due to the greater recourse to Anderson shelters in that year. It is suggested by Arthur (1953) that the ticks are transferred by cats and dogs from the vicinity of hedgehogs' nests to houses and gardens. It was later discovered by my patient that three hedgehogs had recently been seen in his neighbour's garden.

When found on human hosts these ticks should not be removed by traction. The reason is that the anterior segments of the tick are modified into two laterally placed palpi and a central hypostome armed with recurved teeth like the barb on a fish-hook. The insect bites by first making an incision with the cutting organs, then inserting the hypostome. The host's blood is then taken up through a central canal in the hypostome in the same way as fluid is aspirated through a hypodermic needle. If the attempt is made to pull the tick off its host, the hypostome will be left in the skin. The best method of removal is to apply oil liberally to the tick and surrounding skin. This has the dual purpose of blocking up the two laterally placed spiracles through which *Ixodes hexagonus* respires, and of softening the skin of the host.

I am indebted to Mr. E. Browning, of the British Museum (Natural History), for his help in preparing this note.

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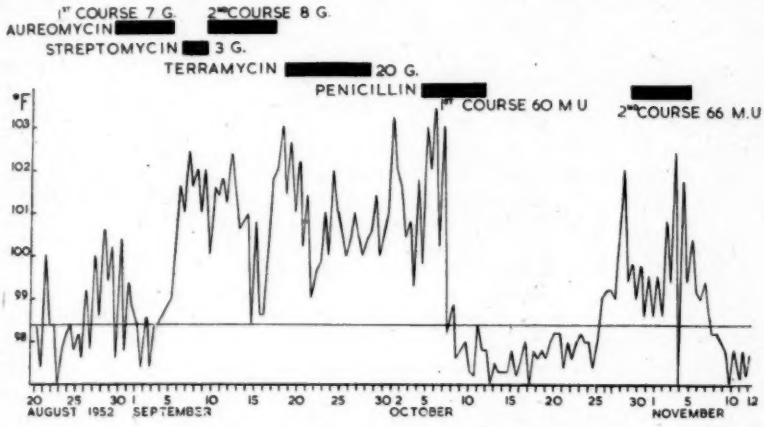
Use of Broad-spectrum Antibiotics in Puerperal Infections

Despite attendant hazards, the ease of administration of the broad-spectrum antibiotics makes their routine use in infectious diseases particularly attractive. During recent months it has been noticeable that most cases of puerperal infection referred to us have already been treated with drugs of the tetracycline group. In many instances these will undoubtedly suffice to control infection. Nevertheless an extensive experience has convinced us that a combination of "sulphatriad," 1.5 g., and penicillin, 250,000 units, six hourly for five days is the most effective treatment, and will control all but a small proportion of cases of puerperal infection (Ramsay *et al.*, 1955).

The following case, referred to us late in the course of the disease, illustrates very clearly the risk of indiscriminate therapy with broad-spectrum antibiotics.

CASE REPORT

A primipara aged 25, following a normal pregnancy and delivery, became pyrexial on the fifth day of the puerperium. On the fifteenth day there was thrombosis of the veins of both legs, and three days later bile in the urine. Three



weeks after this there was further thrombophlebitis, affecting the pelvic veins as well as those of the legs. This was followed by severe jaundice. Blood culture repeatedly gave negative results, and agglutination reactions were negative for *Salmonella typhosa* and *S. paratyphosa* A and B, but positive for *Brucella abortus* (1 in 40) and *Br. melitensis* (1 in 80). As further testing showed no rise in titre, these positive findings were considered to be due to a previous infection. The haemoglobin level fluctuated between 60 and 70%, and there was a polymorphonuclear leucocytosis (up to 16,000 per c.mm. with 90% polymorphs). Urine was sterile except on two occasions when *Proteus vulgaris* was isolated. Liver function tests showed both parenchymatous damage (persistent reversal of the albumin–globulin ratio) and an obstructive element (serum alkaline phosphatase, 40–50 units). This may have been the result of: (*a*) involvement of the portal system in the thrombophlebitic process—a unique complication in our experience; or (*b*) treatment with anticoagulant and/or drugs of the tetracycline group.

The accompanying chart shows that the patient was treated with a succession of antibiotics; the selection of these was entirely random, as no cervical culture had been made before treatment was started. *Proteus vulgaris* was grown from the cervix after the patient was admitted to our unit, but the dramatic improvement which had already occurred following the belated use of penicillin showed that this was not the pathogen. Whatever the causative organism, it was clearly penicillin-sensitive. Had the drug been used at the outset the patient would have been spared a great deal of unnecessary suffering, with, at one period of her illness, grave risk to life.

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Long Incubation Period in Kala-Azar

A patient who presents with fever and splenomegaly will of course be questioned regarding residence abroad; but there is a danger that kala-azar (visceral leishmaniasis) may not be seriously considered in the differential diagnosis if a long period has elapsed since the patient left the endemic area. To emphasize this danger the following two case histories are briefly recorded, for they show incubation periods of *at least* 2½ years and 1¾ years respectively. Sweeney *et al.* (1945) reported a case of Mediterranean kala-azar with "a presumptive latent period of two years," but this is open to question in view of the fact that the patient, an Italian soldier, was taken prisoner in Sicily 14 months prior to the onset of his illness and was detained in Sicily for an unspecified period before being sent to the U.S.A.

CASE REPORTS

Case 1.—A Polish youth went to Southern Italy in 1944, at the age of 19, and remained there for two years. In October, 1946, he came to England, and maintained his usual good health until April, 1949, when he developed fever and lassitude. Four months later he was admitted to hospital, where a diagnosis of kala-azar was made, and he was given two courses of pentamidine injections. Symptoms recurred later and he was admitted to the Hospital for Tropical Diseases, under the care of Sir Neil Hamilton Fairley, in April, 1950. He was found to have a remittent fever, a very large spleen, and a moderately enlarged liver. The haemoglobin was 45%; red cells, 2,360,000 per c.mm.; white cells, 1,200 per c.mm. (neutrophils 38%); total serum protein, 9.7 g. per 100 ml. (albumin 2.6 g., globulin 7.1 g.); formol-gel test strongly positive. The diagnosis was confirmed by spleen puncture, Leishman–Donovan bodies being found in stained films.

Case 2.—An Indian aged 23 left Bombay on May 19, 1952, in order to study in England. On February 7, 1954, he developed fever and malaise, and eight days later he was admitted to the Hospital for Tropical Diseases, under the care of Professor A. W. Woodruff; there he was found to have a remittent fever and a spleen which was just palpable on inspiration. The haemoglobin was 78%; red cells, 4,100,000 per c.mm.; white cells, 2,900 per c.mm. (neutrophils 40%); total serum protein, 7.1 g. per 100 ml. (albumin 4 g., globulin 3.1 g.); formol-gel test negative. The diagnosis was confirmed by sternal puncture; no Leishman–Donovan bodies were found in stained marrow smears, but leptomonads were cultured after 15 days' incubation on N.N.N. medium at room temperature (22° C.).

COMMENT

Kala-azar must be considered in the differential diagnosis of fever and splenomegaly even if a period as long as 2½ years has elapsed since the patient was in an endemic area. The diagnosis should not be ruled out if spleen or marrow smears prove negative; a culture on suitable medium at room temperature must always be carried out in addition. Case 2 demonstrates this point, together with the fact that the formol-gel test may be negative in the early stages of the disease.

I am indebted to Sir Neil Hamilton Fairley and to Professor A. W. Woodruff for permission to publish these cases; also to Dr. D. S. Ridley for the pathological investigations.

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Reviews

TSETSE FLIES

The Natural History of Tsetse Flies. By Patrick A. Buxton, C.M.G., F.R.S. Memoir No. 10 of the London School of Hygiene and Tropical Medicine. (Pp. 816+xx; 165 figures and 47 plates. 84s.) London: H. K. Lewis & Co. Ltd. 1955.

The uneven and imperfect development of the peoples of tropical Africa is largely attributable to the prevalence of diseases affecting men and animals, and of these diseases those conveyed by the tsetse fly have played a major part. Human trypanosomiasis has caused depopulation in certain areas, while the trypanosomiasis of domestic animals has probably exerted an even greater effect on human development than sleeping sickness itself.

An intimate knowledge of the life history and habits of the insect vector is essential for the successful development of control measures. During the past two decades the tsetse has been subjected to intensive study, and it is gratifying to learn that laboratory researches have generally been corroborated by the results of field experiment and observation. The differences between species of tsetse flies are generally rather small and only relative, and this has made it possible to treat the natural history of the genus *Glossina* as a whole. The author rightly insists that the entomology of the tsetse must be related to the epidemiology of the human and animal diseases caused by trypanosomes, and also to the habits of Africans; hence the inclusion of chapters on trypanosomes in tsetse and on the epidemiology of trypanosomiasis as seen by the entomologist.

As regards control measures, insecticides can effect rapid reduction in the number of flies, but it has not proved possible to exterminate them by this means. Direct collection of puparia or an attack on them by the use of parasites has hitherto been unsuccessful. The destruction of game animals has succeeded in several areas, in one on a very large scale. An increase in the density of bush by excluding annual grass fires has been followed by a steady reduction of *G. swynnertoni* or *morsitans*, but has not in itself resulted in extermination. Ruthless clearing of vegetation in the lower part of a river combined with selective clearing of the banks above has eradicated *G. palpalis* and *tachinoides* from parts of West Africa where the dry season is very severe. *G. morsitans* may be exterminated by the destruction of breeding places, and in some areas certain types of hard-pan appear to be essential to the economy of *G. swynnertoni*, which disappears if they are cleared. Human settlement is a valuable method of control; the presence of the villager discourages bush, while in the case of the game tsetse operative factors are disturbance of game and the insect's difficulties in finding a host.

The volume is illustrated by a number of maps and text figures, mostly the work of Major H. S. Leeson, of the London School of Hygiene and Tropical Medicine, and by many excellent photographs. Professor Buxton and his staff are to be congratulated on the production of a work of outstanding merit, which will rank as the standard treatise on the subject for many years to come.

G. Covell.

IDIOSYNCRASY TO DRUGS

Reactions with Drug Therapy. By Harry L. Alexander. (Pp. 301+xii; illustrated. 52s. 6d.) Philadelphia and London: W. B. Saunders Company. 1955.

Toxic effects become apparent with the majority of drugs as the dose is increased. A person in whom these occur with relatively small quantities may properly be said to be hypersensitive. There exists, in addition, however, a different type of response in which a wholly abnormal and usually allergic reaction occurs, as when aspirin in small doses produces urticaria, or when chloramphenicol gives rise to aplastic anaemia. These reactions, which some prefer to call idiosyncrasy, are the subject of this book. The author in his first chapter gives the diagnostic criteria for hypersensitivity, using the term in this latter sense. He proceeds to discuss the mechanisms of it and to outline the main abnormal patterns of reaction. They are comparatively few, but involve important organs such as the skin and liver, and may be fatal if they take the form of shock, periarteritis nodosa, or aplastic anaemia. The remaining three-quarters of the book is devoted to a systematic survey of drugs which have been reported to give rise to these effects. The author has not always found it easy to distinguish this type of response from the effects of overdosage, as when tetra-ethylammonium salts are listed as giving rise to shock.

It is, however, a considerable achievement to have collected the large amount of reliable and up-to-date information which can be found in this book. There is an excellent index. Full references are given to original papers throughout the text, but in places both the names of drugs and of authors are incorrectly spelt. Although it will be used chiefly for reference purposes, it can be read consecutively without undue strain. It is well worth a place on the library shelf.

E. J. Wayne.

DEXTRAN

Dextran: Its Properties and Use in Medicine. By John R. Squire, M.D., F.R.C.P., J. P. Bull, M.D., W. d'A. Maycock, M.D., and C. R. Ricketts, Ph.D., F.R.I.C. (Pp. 91. 15s.) Oxford: Blackwell Scientific Publications. 1955.

This book, written by the four most active British workers on dextran, summarizes in 77 pages of text and 11 of references that knowledge of dextran which had been accumulated by the end of 1954. About a third of the text deals with plasma substitutes in general and with the chemistry of dextran, and the rest with its behaviour in the body, clinical and experimental applications, and the specification of dextran for clinical use.

This is an extremely useful little book, in which accounts of many theoretical and practical problems may be found—and sometimes the answers are given as well. The discussions on the antigenicity of dextran and of reactions following its administration to man are particularly stimulating, while those on the effect of dextran on the erythrocyte sedimentation rate and on blood-grouping and cross-matching are straightforward and surprisingly lucid. There is no separate index, but the table of contents has been enlarged so that all the more important points are indicated.

It is perhaps ungenerous to seek faults in so useful a compendium, but disciples of Sir Ernest Gowers may be excused for recoiling with distaste from such a construction as: "but the causal relationship (as opposed to the association) between marked rouleaux formation and serious complications or fatal outcome of such disease-states one may consider to be undemonstrated"; or from the paragraph of 69 words which contains no stops except four commas, two of which appear to be superfluous. Fortunately such infelicities are unusual, and, though increasing the readers' difficulties, do not completely conceal the author's thought.

George Discombe.

MORPHOLOGY AND FUNCTION OF NEUROGLIA

Neuroglia, Morphology and Function. By Paul Glees, M.A., D.Phil., M.D. (Pp. 111+xii; illustrated. 25s.) Oxford: Blackwell Scientific Publications. 1955.

The study of the neuroglia has absorbed histologists ever since silver stains were introduced, partly because, as Hortega pointed out, their demonstration has such an aesthetic appeal to the neurological histologist. The division of the cells into the types at present accepted is quite recent, and their functions are consequently speculative. Some, such as the astrocytes with their perivascular sucker feet and their branching dendrites, seem to have a specialized function, but so far we have no idea what it is. In consequence experimental histologists and physiologists have taken up the subject, and now, in tissue culture, the cells

are seen to have an activity which is not reflected in the beautiful dead stained preparations that we have all seen and admired. There is, for instance, the slow rhythmic movement of some of the oligodendroglial cells, and there are the alterations in astrocytes and in microglia which occur in disease and in response to experimental changes in the condition of the brain.

It has not yet been suggested that neuroglia may have any part to play in the resting electrical potentials which occur in the brain, but, on the other hand, literally nothing is known of the function of the astrocyte with its elaborately branching structure.

It is surprising that, while there have been such diverse and fundamental discoveries about the function of the neurone, until now the study of the equally complex neuroglia has been confined to demonstration of its morphological characteristics. It is therefore most timely that Dr. Paul Glees should have contributed a book with the title *Neuroglia, Morphology and Function* to the series of short monographs which appear in the American Lecture Series, even if the section on function is of necessity dominated by that on morphology.

The monograph is very short and it is beautifully illustrated, so that those with an eclectic interest will have pleasure in its reading. The expert will find an inclusive bibliography and a critical survey. Dr. Glees writes well and succinctly, and his present review can be warmly recommended.

DENIS WILLIAMS.

SURGERY OF THE SYMPATHETIC SYSTEM

Surgery of the Sympathetic. By Alexander Lee McGregor, F.R.C.S., M.Ch. (Pp. 192; illustrated. 30s.) Bristol: John Wright and Sons Ltd. 1955.

Several books have been written on the surgery of the sympathetic nervous system. Gask and Ross produced their beautiful monograph in 1934. It remains unsurpassed as a model of clarity of thought and expression; but so much new ground has been broken since its publication that a new edition is sorely needed. White, Smithwick, and Simeone have recently revised their work on the *Autonomic Nervous System* and it is the most helpful reference book and guide to workers in this field. Its size is perhaps a deterrent to the occasional operator, who might welcome a short practical guide. It was therefore with pleasant anticipation that one opened Lee McGregor's new book, particularly as so many of us are grateful to him for his book on surgical anatomy which has been helpful in the past. The preface promises that the book will endeavour to make the practical applications clear. The standard operations are well described, but the more important aspect of the indications for operation and the selection of the patients likely to benefit is less successfully done. In this important way the book is disappointing, although in other ways it is valuable. A great deal of new work is described or referred to in a stimulating manner. The book is much more helpful as a review of recent advances in the physiology or surgery of the sympathetic than as a practical guide.

J. B. KINMONTH.

TEN TEACHERS

Midwifery. By Ten Teachers under the direction of Frederick W. Roques, M.D., M.Chir., F.R.C.S., F.R.C.O.G. Edited by Frederick W. Roques, John Beattie, and Joseph Wrigley. 9th edition. (Pp. 607; illustrated. 32s. 6d.) London: Edward Arnold Ltd. 1955.

Several generations of students have been grateful for a textbook on midwifery which, besides being precise and didactic, provides views which will be whole-heartedly accepted by at least ten London teachers. The ninth edition presents a striking innovation which will be regarded as inevitable by many and deplored by a few. The chapters devoted "to the health and disease of the newborn infant" have been entrusted to a paediatrician, Dr. Hart. These chapters are truly excellent, but contain no material which should not have been within the knowledge and experience of the obstetrical authors. The tradition of the book has been broken before the implications of all the factors involved have been fully weighed.

The section on tuberculosis complicating pregnancy is perhaps inadequate, and no mention is made of B.C.G. vaccination of the infant born to a tuberculous mother. The statement that the level of haemoglobin during pregnancy cannot be raised above 70% is incorrect; no mention is made of fibrinogenopenia; and one or two minor inaccuracies occur in the index.

These trifling criticisms cannot detract from the great value of this book, which has passed through eight editions and been reprinted eight times in less than forty years. The subjects are treated in a logical order, the writing is succinct, the value of each word has been carefully weighed, and the illustrations are adequate. The teaching is fairly conservative and is remarkably representative. The type is excellent and the paper reasonably thin, so that this book is little more than half the size of some other textbooks with approximately the same number of words. It may be safely conjectured that this edition will become exhausted within the normal span, for this book, of three years.

G. W. THEOBALD.

CARDIAC EMERGENCIES

Cardiac Emergencies and Heart Failure: Prevention and Treatment. By Arthur M. Master, M.D., Marvin Moser, M.D., and Harry L. Jaffe, M.D. (Pp. 203; illustrated. 28s.) London: Henry Kimpton. 1955.

This little book discusses the prevention and treatment of these common events. Sudden and serious derangements of function and development of disease are very much a feature in the cardiovascular system. All too often a grave situation has to be faced with the life of the patient in the balance. Diagnosis is very important, and usually has to be made on the bare clinical findings. In this book there is just enough about diagnosis to give the outline of the clinical picture so that the grounds for treatment are made clear. Clarity and brevity are the chief virtues and all is to the point. The authors give their reasons for this and that, based on their great experience. Italic print marks statements of special importance. Naturally the use of drugs plays a particularly large part. But the American names of many of them are not familiar over here, and it would have been more useful if some of the British equivalents could have been included; though in these days to keep pace with the nomenclature of the vast number of new and potent drugs is very difficult, even in one country alone. In this book the authors restrict the use of anticoagulants to certain selected cases only of coronary disease. Surgical measures are fully described when needed, and dangers and difficulties made clear.

This is a most sane and practical book and can be well recommended. There are nearly 350 references, which can fill in any gaps (really there are none), a full index, and a fair number of cardiograms.

TERENCE EAST.

DENTAL X-RAY DIAGNOSIS

Dental and Oral X-ray Diagnosis. By A. C. W. Hutchinson, D.D.S., M.D.S., F.D.S., F.R.S.E. Foreword by Sir Sydney Smith, C.B.E., M.D., F.R.C.P., D.P.H. (Pp. 524+xii; 946 illustrations. 75s.) Edinburgh and London: E. and S. Livingstone Ltd. 1954.

This is a well-illustrated book giving the *x*-ray appearances of all the commoner conditions likely to be met with in the jaws, in addition to many less well known. The author is to be congratulated on collecting such a remarkable collection of illustrations from many different sources. The aetiology and pathology and clinical features are well discussed in the text accompanying the illustrations, and the book should prove of great value for reference, both to the postgraduate student and to the practitioner.

A. B. MACGREGOR.

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LIPIDS AND ATHEROMA

Evidence on the association between lipid metabolism and the development of atheroma continues to accumulate. One of the main obstacles to a fuller understanding of the problem is the lack of any means of detecting atheroma during life except by its local complications. Atheroma can be found at necropsy in people of all ages. A careful histological study made recently by P. H. Lober[1] in a series of 536 unselected necropsies showed that coronary atheroma is the end result of a continuous process of infiltration and thickening of the intima and reduction in the size of the lumen which begins at birth and progresses at an almost uniform rate until the ninth decade. There are thus no "normal controls" with whom to compare diseased subjects. In practice, the occurrence of a coronary thrombosis is the most reliable criterion of the existence of atheroma during life, and it is probably the most important manifestation. For the purposes of clinical investigation it is customary to compare survivors of coronary thrombosis with apparently healthy people of the same age and sex. Although some authorities[2] consider that the occurrence of thrombosis is not necessarily related to the severity of the atheromatous lesions, Lober[1] found that symptoms of coronary disease had been present during life only in the patients with most severe sclerosis affecting all three main arteries, regardless of the age at death.

Evidence of the importance of cholesterol metabolism in the development of atheroma is manifold. Atheromatous plaques contain much cholesterol.[3] The blood cholesterol level in man is higher than in the other mammals, which are relatively immune to the disease.[4] Most methods of inducing atheroma in experimental animals depend upon high cholesterol feeding.[5] Conditions associated with hypercholesterolaemia in man predispose to severe atheroma. The mean blood cholesterol level in patients with coronary atheroma is higher than in healthy subjects of the same age and sex, though there is considerable overlap between the two groups; fewer than half of the individual patients have higher levels than the average level of the controls.[4] The deposition of cholesterol in the intima does not therefore depend solely upon the concentration of cholesterol in the blood.

Cholesterol and other lipids are insoluble in water and are transported in the plasma in combination with proteins. These lipoproteins are water-soluble. They are separable into alpha and beta fractions by electrophoresis and carry virtually the whole of the serum cholesterol, approximately 70% in beta-lipoprotein (Cohn's fractions I+III) and 30% in alpha-lipoprotein (Cohn's fractions IV+V+VI).[6 7] J. W. Gofman and his colleagues[8 9] have separated the lipoproteins into nine or ten groups, arranged numerically according to their rates of flotation in the ultracentrifuge. The greater part of the serum cholesterol is carried in the S_f 3–8 class (3–8 Svedberg units of flotation). Phospholipids are thought to play a part in stabilizing the colloidal dispersion of cholesterol,[10] so that an increase in the ratio of total cholesterol to phospholipid in serum (the C/P ratio) may favour the deposition of cholesterol. Thus changes in the physico-chemical properties of the lipoprotein complexes may be a factor in the development of atheroma. In fact changes in the lipid and lipoprotein pattern of the serum are commonly found in patients with coronary atheroma. The concentration of cholesterol is increased in beta-lipoprotein and reduced in alpha-lipoprotein.[6 7] The C/P ratio tends to be raised.[6–11] The concentration of S_f 12–20 and 35–100 lipoproteins is increased, though these contain only 10% of the total serum cholesterol.[9] What determines the entry of lipids into the intima is the subject of much controversy. After reviewing the evidence, L. N. Katz and J. Stamler[5] conclude that the process is one of filtration.

Age plays an important part in the development of atheroma. The cholesterol level is low

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in umbilical-cord blood, but reaches adult levels in infants soon after birth.[4] The blood cholesterol level tends to rise gradually with age until the sixth decade in communities which live on a diet which is fairly rich in fat, but does not continue to rise so late in life in those accustomed to a low fat intake.[12] The influence of sex is also striking. Coronary atheroma is more prevalent in men than in women. According to Lober's studies,[1] the sex-difierentiation, as shown by histology, begins in infancy and continues into old age. Females follow 10 to 20 years behind males in this respect. This conforms with the greater susceptibility of males to noxious influences from the time of conception.[13] Coronary thrombosis is about twenty times as common in men as in women under the age of 40 years,[14] and male patients in the fourth decade show a greater excess of blood cholesterol over their controls than patients of either sex in any other age group.[11] The existence of the sex difference before puberty and its persistence after the menopause might suggest that endocrine secretions play no part, but there is evidence to the contrary. The concentration in the serum of S_f 12–20 lipoproteins rises between the age of 25 and 30 years in men and then remains constant; in women there is no marked increase between the age of 25 and 30 years, but the concentration increases slowly to equal that of the males in the sixth decade.[14] The incidence of coronary thrombosis in women increases after the menopause, so that the sex incidence becomes equal after the age of 70 years.[11] Women develop more severe degrees of coronary atheroma at an earlier age after oophorectomy.[15] In diabetic patients this striking sex difference is not found.[16] These findings suggest that the physiology of the female reproductive period may afford some protection against atheroma. Further evidence of this is that the administration of oestrogens produces a fall in blood cholesterol level in patients with atheroma and corrects the abnormal lipid and lipoprotein pattern in the serum. The administration of androgen to healthy men induces changes in these patterns similar to those associated with atheroma and enhances those already present in disease. The effect of androgens is more powerful than that of oestrogens.[6]

In so far as diet is concerned in aetiology the fat content of the food is the important factor rather than the cholesterol content. Ancel Keys in particular has studied this problem.[12] Populations living habitually on low fat diets tend to have lower serum cholesterol levels and a lower incidence of atheroma than those existing on a high fat intake. This does not seem to be due to racial influences, since the same differences exist between poor and wealthy communities of the same nationality. G. V. Mann and his associates have also studied this problem. In articles published in the *Journal* this week (p. 1008) and elsewhere[17] they cast some doubt on the importance of fat intake and suggest that the lipid and lipoprotein concentrations in the serum may be determined by the balance of calorie intake and energy expenditure. It is well known that obesity predisposes to severe atheroma,[18 19] and the degree of atheroma is less in wasted patients dying from malignant disease than in those dying from other causes.[1]

The role of lipaemia in the pathogenesis of atheroma is less certain. J. R. Moreton[20] introduced the concept of cholesterol-bearing chylomicrons accumulating in the blood after fatty meals and impinging upon the arterial intima, depositing lipids therein. However, persistent idiopathic hyperlipaemia, unlike hypercholesterolaemia without hyperlipaemia, does not predispose to atheroma.[21] Moreover, Gofman and his colleagues[8] found that chylomicrons (S_f values greater than 75) contained only 5% or less of cholesterol and were not particularly associated with atheroma. Nevertheless, alimentary lipaemia tends to be greater in intensity and duration in people over the age of 50 years[22] and in patients with coronary artery disease.[23] Alimentary lipaemia can be abolished within a few minutes by the injection of heparin, which leads to the appearance of a clearing factor in the globulin fraction of the plasma. This factor appears to act as a lipolytic enzyme which releases fatty acids from lipoproteins. It also increases the electrophoretic mobility of alpha- and beta-lipoproteins, converts lipoproteins of high S_f values into those of successively lower values down to S_f 10, and relieves anginal pain.[24–26] It is not certain whether heparin plays a part in the physiological transport of fat. Attempts to demonstrate it in the plasma have not so far been successful,[27] but clearing activity has been demonstrated in the plasma of rats after feeding with olive oil.[28] H. W. Fullerton has shown[29] that the coagulability of the blood is increased after a fatty meal, and it is conceivable that this might be a factor in initiating the development of mural thrombi, which J. B. Duguid[30] believes are the origin of atheroma in many cases. Whether or not lipaemia is concerned in the pathogenesis of atheroma, it appears to provoke anginal attacks. It has recently been shown[31] that anginal pain can be induced in patients with coronary atheroma at a period of 3 to 5 hours after a fatty meal, when lipaemia is maximal. The pain was accompanied by electrocardiographic changes and could not be induced by high carbohydrate or high protein meals without a high fat content.

None of this new knowledge helps greatly in the prevention and treatment of atheroma. Even complete

elimination of fat from the diet reduces the blood cholesterol level by a mean of only 15%,[32] though moderate fat restriction may reduce the concentration of S_f 12–100 lipoproteins.[9] The administration of sitosterol, a non-absorbable plant sterol, is said to interfere with the absorption of cholesterol, but does not reduce the blood cholesterol level by more than a mean of 16%.[33] In any case only a limited amount of cholesterol is absorbed, and it has been calculated from isotopic studies that approximately 2 g. of cholesterol is synthesized daily, whereas the average diet contains about 400 mg. daily.[34] The same limitation applies to the restriction of dietary fat. Phenylethylacetic acid is said to interfere with the synthesis of cholesterol, and it has been claimed by French workers that the blood cholesterol can be reduced by as much as 40% in cases of hypercholesterolaemia[35] by means of this drug. In spite of the striking effect of oestrogens upon the serum lipid and lipoprotein pattern, no significant effect upon anginal symptoms has been achieved by their administration, and they have the disadvantage of inducing feminization and other side-effects. The outlook is therefore still bleak. We cannot stave off increasing age. We are already warned of the dangers of smoking. It appears that some of us must also forgo many of the pleasures of eating and, as men, unsex ourselves if we wish to live our threescore years and ten.

HOSPITAL MEDICAL STAFFING

The medical staffing of hospitals has presented constant difficulties ever since the Health Service started. Indeed, a previously free service of independent units with a variety of staffing needs could hardly be expected to conform with ease to nationalization overnight, nor could an established way of professional life be suddenly changed on an appointed day. But underlying the whole problem is the fact that in recent years the demand for medical staff in hospitals has greatly increased, a demand which has come from progress in medicine itself and intensified by the development of the services provided by many hospitals throughout the country. Thus the demand has been for quality as well as quantity, and the supply has been unable to keep pace. It is significant that the number of doctors qualifying each year is fewer than the number of house-officer posts, and the shortage extends upwards through the whole staffing structure below consultant rank. It was to find a solution to the problem of hospital staffing that the B.M.A.'s Central Consultants and Specialists Committee set up in 1953 a subcommittee under Professor G. I. Strachan. Its proposals,[1] approved by the Representative Body this year, are now in the hands of the Joint Consultants Committee, which, in turn, is discussing the question with the Ministry of Health.[2]

Apart from those already mentioned, there are many complex, and to some extent interrelated, contributory causes of the shortage of hospital staff, of which it will suffice here to mention a few. There has been the difficulty of attracting men, looking for a settled future after their National Service, back into what appears to them to be an unattractive hospital service offering a reduction of salary compared with Service pay, uncertain prospects, and, except in a few cases, no married quarters. In the past it was much easier for a young doctor to move freely from hospital to general practice, and vice versa, or to combine the two types of work; and the young doctor was then less intent upon security. The Strachan Committee was convinced that the rigidity of the existing hospital staffing structure, the lack of equality in promotion prospects, and the growth of the hospital service as a separate entity largely closed to practitioners in other forms of work underlay most of the present difficulties. To the list of problems must also be added those of the 3,000 senior hospital medical officers—nearly half as many as the graded consultants and far from being reduced in number as was originally intended—who seem to have justice in their complaint that they are in many cases doing consultant work with but few prospects of promotion from what in practice has become a dead-end grade.

Even this brief outline makes it clear that the troubles of hospital staffing need some more radical cure than the somewhat *ad hoc* treatment that they have had up to now. The Strachan Committee's long-term proposals, which, as a preliminary report[2] of a meeting between representatives of the Joint Committee and the Ministry seems to show, have been adopted in the main by the Joint Committee, are certainly realistic. In summary they are as follows. The Committee advocates that in every hospital the volume of work which should be done only by consultants should be determined and the establishment adjusted accordingly. The Committee thinks that this may well show that some redistribution of, and an increase in, consultants is necessary. However, it is on the intermediate grade of hospital staff, at present made up of what seems to be a superabundance of different grades, that the Committee has focused its chief attention. It proposes that there

[1] *British Medical Journal Supplement*, 1955, 1, 177.
[2] Ibid., 1955, 2, 51.

should be only one intermediate grade between house officer and consultant, that it should be in three levels of seniority, and that appointments to it should be according to the needs of the hospital and the work to be done. It could be implied from this that the Committee feels that in future it is the post that should be graded and not the individual. At all events it urges that the present policy of specifying a certain category of medical staff for the training of consultants and of fixing hospital establishments wholly in relation to prospective consultant vacancies should be abolished. It is envisaged that the new intermediate grade should undertake much of the regular medical, surgical, and other treatment in hospital, and that it should become "the training ground for all those who aspire to consultant rank." A further and important proposal is that part-time appointments in the intermediate grade should be encouraged so that general practitioners should have an opportunity of working in hospital and even eventually of becoming consultants. All existing senior hospital medical officers, it is recommended, should be redistributed between the consultant establishment and the senior level of the new intermediate grade according to their qualifications and experience. Likewise senior registrars and registrars should be redistributed within the various levels of the grade.

The Strachan Committee proposals themselves represent a marriage of some differences of opinion among the various interests concerned, arrived at after considerable debate. What the outcome of the present discussions with the Ministry will be remains to be seen. Whatever the final conclusions, it is to be hoped that the opportunity will not be missed of rearranging hospital staffing so that in future junior posts will offer reasonable prospects of a career either within the hospital service itself or in combination with other medical work, and also come to be looked upon as proper and useful stepping-stones to other forms of practice. It cannot be said that these conditions apply at the moment.

MITRAL VALVOTOMY

Routine surgical treatment of mitral stenosis has now been practised for five years,[1–5] and a present operative mortality of about 5% must be accepted. An appreciably lower figure can be expected only if very rigid criteria are applied and surgery refused except in the most favourable cases. Improvement occurs in three-quarters, and in most of these is very great. Many severely disabled patients have returned to normal life.

In our opening pages this week Dr. C. Baker, Sir Russell Brock, and Dr. M. Campbell report a follow-up of 45 patients for three years and more after mitral valvotomy at Guy's Hospital. These include the first patients operated on in Britain and many with very severe disease, so may not be quite equivalent to a similar series operated on to-day. The assessment has been thorough and the results are classified strictly. At the end of one year 38 patients had good or excellent results, at the end of two years 35, and at the end of three years 29, the others having deteriorated or died. In the series reported by Mr. W. P. Cleland and his colleagues a few weeks ago[4] there were also a small number who deteriorated after an initial improvement. Nevertheless, as emphasized in a leading article then,[6] the improvement obtained by operation is usually maintained. As would be expected, the improvement resulting, and particularly the long maintenance of this improvement, depend on the state of the mitral valve at operation, and on the alteration in this state which the surgeon is able to achieve. This is clearly shown by the detailed analysis in Baker, Brock, and Campbell's present article. They found that the best correlation between a lasting good result and any factor that could be assessed at the time of operation was with the surgeon's account of his procedure. An accurate assessment of the state of the valve can be made at operation. Inability to see it is surprisingly little disadvantage. Palpation with the index finger determines the size of the orifice, the mobility of the cusps, the thickness of the edge, and the presence of calcification; after enlargement, if necessary, the chordae tendineae can be felt and thickening appreciated. The presence of a regurgitant stream can be nicely assessed, and its volume and rate judged—more easily than can be done in the post-mortem room. A comparison can be made after valvotomy, especially between size of orifice and extent of regurgitation, if any. In most patients of this series the estimated diameter of the valve before valvotomy was 1 cm. or less. This is a critical size above which simple stenosis seldom causes significant disability; marked symptoms when this size is exceeded must at least in part be due to mitral regurgitation, so that complete relief from valvotomy cannot be expected. This was confirmed by the operative findings and by the results, which were least good when the diameter was greatest. The results were also closely related to the state of the valve after valvotomy. The estimated size of the orifice is perhaps no more than an indication of its function, but it is a measurement of considerable importance in prognosis. In 18 of the 45 patients an opening of 3 cm. or more could be achieved, and all except one of these had good or excellent results. In 14 of the patients

[1] Baker, C., Brock, R. C., and Campbell, M., *British Medical Journal*, 1950, **1**, 1283.
[2] —— —— —— and Wood, P., ibid., 1952, **1**, 1043.
[3] Bedford, D. E., Sellors, T. H., and Somerville, W., ibid., 1953, **2**, 1059.
[4] Cleland, W. P., Davies, L. G., Goodwin, J. F., Hunter, J. D., and Steiner, R. E., ibid., 1955, **2**, 575.
[5] Logan, A., and Turner, R., *Lancet*, 1953, **1**, 1007.
[6] *British Medical Journal*, 1955, **2**, 607.
[7] Margary, F. R., ibid., 1951, **1**, 856.
[8] Sellors, T. H., *Brit. med. Bull.*, 1955, **11**, 208.

some degree of mitral regurgitation was noted by the surgeon. Calcification was present in nine of these; three have died and only six had good results. Regurgitation was caused by the operation in six cases, but three of these have done well. If the surgeon is satisfied at the operation, anxiety about the patient's post-operative state is unusual, and the physician is satisfied with the later result. Technical difficulties at operation may lead to a poor result or to operative death[4]; for example, there may be tearing of the atrial wall, ventricular fibrillation, coronary artery occlusion by sutures, cerebral or peripheral embolism by thrombus or calcific particles, the production of severe incompetence, or rupture of a chorda. Baker, Brock, and Campbell have found that pre-existing atrial fibrillation does not militate against a successful result—in fact the state of the valve is much more important than the rhythm. As in other series, atrial fibrillation often appears shortly after operation; it usually reverts spontaneously or with treatment, but, if persistent, constitutes a set-back. Pulmonary hypertension can be expected to be reduced, typically to about half the former level, the fall occurring over many months; a good result is usually obtained in patients with severe hypertension. The size of the heart does not seem to influence the result, and although it may decrease it often does not change. Recurrent or continued rheumatic activity, sometimes difficult to assess, may lead to the valve becoming stenosed again. F. R. Margary[7] found that stenosis was due to organization of repeated fibrin deposits and suggested recurrence was possible. Although re-stenosis is rare, it now seems that occasionally a second operation is indicated. Mild fever and precordial pain a few weeks after operation may not be due to rheumatism, but may be simply a reaction to pericardotomy.

Most surgeons use a similar technique for mitral valvotomy (this term has now replaced commissurotomy and valvulotomy in Britain), and T. Holmes Sellors has recently given a full account of the operation in a special number of the *British Medical Bulletin* devoted to cardiac surgery.[8] The heart is approached by left postero-lateral thoracotomy through the bed of the fifth rib, which may be resected. The lung is retracted and the pericardium opened by a vertical incision, usually just anterior to the phrenic nerve. The valve is usually approached through the left atrial appendage (left auricle) by inserting the index finger, which it fits snugly. Haemorrhage is controlled by a clamp or a purse-string suture. If the appendage is small or obliterated by thrombus the approach may be through the superior pulmonary vein or directly through the atrial wall. The valve can very often be split by digital pressure, though sometimes this must be very forcible. Disruption of both commissures is ideal, but the surgeon must often be content with the lateral only. The frequency with which a knife is used varies in different hands, and the variety of patterns available suggests that the ideal has not yet been invented. The atrium is repaired by simple sutures and the pericardium loosely closed.

INFLUENZA VIRUS C

In the last fifteen years two viruses, virus A and virus B, have been firmly established as the cause of influenza. These two viruses, antigenically distinct, have now been recovered from cases of influenza all over the world.[1] In 1947 R. M. Taylor in New York isolated an "influenza-like virus" from a patient with a mild febrile respiratory illness.[2] A year later T. Francis and his colleagues at Ann Arbor, Michigan, recovered a similar viral agent from a case of mild respiratory disease during the course of an influenza A epidemic.[3] Both agents were similar to each other, resembled both virus A and B in a number of ways, but were serologically distinct from them. The term influenza virus C was proposed.[3] Virus C has now been reported from a number of countries, and in this week's issue of the *Journal* Drs. B. E. Andrews and J. C. McDonald (p. 992) and Dr. N. R. Grist (p. 994) report its presence in Great Britain.

From the epidemiological aspect it would appear that virus C has been mildly active for a number of years.[3] Serological tests in the United States indicate that infection is widespread and acquired early in life, antibody levels in the population rising sharply from a fairly low level at 3–5 years of age.[4,5] From the papers we now publish this seems to be true of Britain also. The number of reports of concurrent infection with this virus and the other two is of some interest. Francis *et al.*[3] showed that virus C had been active in 1947 during the influenza A outbreak in a children's home, and reports of its occurrence with virus B have also been made.[6,7] Infection of adults and children with both virus A and C in Glasgow in 1954 is reported by Grist this week.

The place of virus C in the epidemiological pattern of influenza is not yet clear, but in general terms perhaps virus A stands at one end of the scale of a related group of viruses, being in the main responsible for major outbreaks and epidemics; virus B occupies an intermediate position, essentially endemic and causing scattered outbreaks annually, but still capable of causing epidemic disease as it did in Britain in the winter of 1945–6[8]; at the other end of the scale is virus C, associated with a milder, widespread, and in many cases subclinical infection. As an infective agent virus C behaves like an influenza virus, although it is quite distinct serologically from both A and B. There are significant differences in its growth in the fertile egg, in the haemagglutination reaction, and in its pathogenicity for laboratory animals.[9]

[1] Isaacs, A., *Brit. med. Bull.*, 1953, **9**, 208.
[2] Taylor, R. N., *Amer. J. publ. Hlth*, 1949, **39**, 171.
[3] Francis, T., *et al.*, *Science*, 1950, **112**, 495.
[4] Davenport, F. M., *et al.*, *J. exp. Med.*, 1953, **98**, 641.
[5] Hilleman, M. R., *et al.*, *Bull. Wld Hlth Org.*, 1953, **8**, 613.
[6] Hennessy, A. V., *et al.*, *Amer. J. Hyg.*, 1953, **58**, 165.
[7] Gerber, P., *et al.*, *Proc. Soc. exp. Biol. (N.Y.)*, 1952, **81**, 624.
[8] Dudgeon, J. A., *et al.*, *Lancet*, 1946, **2**, 627.
[9] Minuse, E. J., *et al.*, *J. Lab. clin. Med.*, 1954, **43**, 31.
[10] Rowe, *et al.*, *Proc. Soc. exp. Biol. (N.Y.)*, 1953, **84**, 570.
[11] Hilleman, M. R., *et al.*, *Amer. J. publ. Hlth*, 1955, **61**, 163.
[12] Zaiman, E., *et al.*, *Lancet*, 1955, **2**, 595.

Clinically there is nothing spectacular about virus C; indeed, its chief characteristic would seem to be its unobtrusive behaviour in respiratory disease as a whole. The few cases that have been observed in the United States so far have had symptoms referable to the upper respiratory tract with little or no fever and have been termed "mild influenza." This is in keeping with the findings of Grist and of Andrews and McDonald.

The recognition of influenza C is largely due to developments in virological laboratory methods, and as they continue it is likely that even more types of "acute respiratory disease" will come to be distinguished from each other. Only in the last few weeks cases of infection with the newly recognized A.P.C. viruses[10 11] have been reported in Great Britain,[12] and, though it may not be of much concern to the patient precisely which of these viruses he or she has succumbed to, the knowledge is of value in building up a comprehensive picture of the epidemiology of respiratory disease.

VISIT OF RUSSIAN DOCTORS

The six eminent representatives of the Russian medical profession who are guests of the British Medical Association were met at London Airport by the Secretary of the Association, the Editor of the *Journal*, and Dr. Grey-Turner, Assistant Secretary, last Sunday, and were entertained by the B.E.A. and their chief medical officer, Dr. A. Buchanan Barbour, before leaving for their hotel in London. On Monday they were entertained at luncheon at B.M.A. House, and in a few remarks of welcome Dr. E. A. Gregg, Chairman of the B.M.A. Council, said: "It is our hope, too, that through the opportunities of personal contact provided in this way we may be able to make some contribution to the breaking down of barriers and the achievement of that mutual understanding which is essential to the peace of the world." Professor S. A. Sarkisov, replying in English, said they, too, attached great importance to the establishment of personal contacts. After lunch the guests made a tour of B.M.A. House. In a remarkably short time our Russian visitors made their British hosts aware of their innate friendliness and vivid interest in various aspects of medical work in this country. This week they are visiting various institutions, including St. Bartholomew's Hospital, the Middlesex Hospital, the Postgraduate Medical School at Hammersmith, the National Institute for Medical Research, the Imperial Cancer Research Laboratories, and the Wellcome Foundation. They will be entertained at dinner by the University of London and the Government, and at lunch by the Society of Apothecaries and the Royal College of Surgeons. The Medical Women's Federation is giving dinner to the two women members of the delegation, and the College of General Practitioners to the four men. Next week the visitors will travel north to Edinburgh and Glasgow, and on their return will visit Birmingham, Cambridge, and Oxford. Before leaving for Russia they will have luncheon at the Royal College of Physicians in London and a farewell dinner with the Council of the B.M.A.

Professor S. A. Sarkisov has published work on the function of the cerebral cortex, Dr. L. G. Bogomolova on problems of blood transfusion, Professor M. N. Foteeva on radioactive isotopes and radiation sickness, Professor G. F. Gause on antibiotics, and Professor L. F. Larionov on the pathology of cancer, while Professor V. V. Kovanov, the one surgeon in the party, is completing his preparation of an atlas of topographical anatomy: the posts held by the delegation were given in the *Journal* of August 6.

This visit shows once more that when governments allow an easing of tension professional groups of different countries are eager to meet each other to discuss common problems and to exchange information, and to make those personal contacts which help to brush away the cobwebs of misunderstanding. Of no profession is this truer than of medicine and of the natural sciences which are its foundation.

THE W.M.A. AND MEDICAL ETHICS

Three weeks ago the French Ordre des Médecins held in Paris an international conference on medical ethics, and an account of this is given in this week's *Supplement*. In France membership of the Ordre des Médecins is compulsory. The voluntary organization of doctors in France is La Confédération des Syndicats Médicaux Français, which is the member association of the World Medical Association. It appears that no member of the W.M.A. was represented at this conference on ethics, and the W.M.A. had in fact advised its members not to attend.

The conference is reported so that medical men may know the views expressed there on a matter which is fundamental to the professional life of the individual doctor and of his representative organizations. An attempt will probably be made, we are informed, to create an international medical ethics organization. No one, of course, would question the right of any group of doctors to take such action. But the W.M.A. has since its inception been recognized as the one international body which can speak with an authoritative voice on medical ethics, and its Code of Ethics and Declaration of Geneva have been widely adopted all over the world. It is much to be hoped, therefore, that those responsible for the recent Paris conference will not proceed with the idea of setting up another international organization on medical ethics. The W.M.A. is now co-operating with the International Committee of the Red Cross, the International Committee of Military Medicine and Pharmacy, with the assistance of the World Health Organization, in studying the complicated question of international medical law. This must be based on medical ethics, and so on the international code of the W.M.A. Duplication of effort and rivalry in this field is neither necessary nor desirable.

EMERGENCIES IN GENERAL PRACTICE

COMA IN HYPOPITUITARISM

BY

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Chronic hypopituitarism is due to the destruction of the anterior lobe of the pituitary. The most frequent cause of this destruction is an ischaemic necrosis of the anterior lobe which occurs in women at delivery as a result of very severe obstetric haemorrhage or shock, such as from a retained placenta. (Peculiarly enough, severe haemorrhage in men does not lead to necrosis of the pituitary.) In other cases the gland may be destroyed by an adenoma or a cyst, or less often by an inflammatory condition such as sarcoidosis, gumma, etc. These tumours and granulomas can occur in either men or women, and they give rise to all the standard signs of hypopituitarism, but usually with additional symptoms due to local pressure in the region of the chiasma and hypothalamus. The post-partum type, being free from this complication and being the most common form of severe hypopituitarism, is taken as the example for the present account, but the description of the clinical aspects and of the coma is applicable *mutatis mutandis* to other varieties of hypopituitarism in men and women.

From the time of the delivery the patient is in permanent ill-health, and does not menstruate again. After some years she is liable to have an episode of coma. Sometimes the coma leads to death in a few hours or in a day or two. Sometimes the patient improves for a time but relapses and dies a few days later. In other cases she recovers gradually in two or three days, but even then the prospect is not good, because for the rest of her life she is liable to further episodes of coma at intervals varying from a few weeks to a few years. Nearly all the patients die in coma; some in the first attack, some after five or ten recurrences.

Preliminary Examination

It is convenient for purposes of description to follow the usual course of investigation of any comatose patient.

The doctor, on arriving at the house, makes a few preliminary inquiries. He is told that the patient has been a chronic invalid for several years but has not bothered to see a doctor recently. For two or three days she has been unusually drowsy or may have been vomiting, and within the last few hours she has lapsed gradually into coma.

In many cases the patient is lying curled up on her side like a foetus in the uterus; her arms and legs and neck are held firmly flexed. Less commonly all the muscles are flaccid and she lies on her back. The coma may be very deep, but there is often some response to painful stimuli: she may grunt or retract a limb. Examination of the nervous system gives variable results; the essential point that emerges is that there is no hemiplegia.

A more discerning inspection of the patient shows certain features of importance. The skin has a soft texture and is not scaly: it is usually dry, but there is heavy sweating in some cases. The face is peculiarly white, though the mucosae are not correspondingly pale. The eyebrows are thin, particularly in their outer halves, and there may be some puffiness around the eyes and across the bridge of the nose. The head hair is of normal amount and colour and is soft.

The pulse is usually weak; it may be fast, normal, or slow. The blood pressure is subnormal in most cases. The respirations tend to be shallow. The temperature may be raised, normal, or low. The other routine examinations usually give negative results.

At this stage the aetiology of the coma may seem quite obscure. However, if the doctor is aware of the possibility of hypopituitarism as a cause of coma, his suspicions will have been aroused by the appearance of the patient. There are then four easy investigations which will give an almost immediate presumptive diagnosis.

Diagnosis

The most important and most conclusive investigation is simply to look at the vulva. In hypopituitarism severe enough to produce coma there is no hair on the mons and only a few short hairs on the labia majora. If the patient has no pubic hair, confirmation of the diagnosis of hypopituitarism can be obtained from two sources. Firstly, the thyroid is too small to palpate; a palpable gland almost negatives the diagnosis. Secondly, there is atrophy of the genital tract. The vulva and vagina are atrophic, the cervix is very small and may be little more than a dimple, and the uterus is correspondingly small; these findings are very significant if the patient is under 45, though they are obviously of much less importance in a woman of 60. When the existence of hypopituitarism has been reasonably clearly established from the physical examination, the last step is to question the relatives about the details of the clinical history, because this will usually clinch the diagnosis.

For the benefit of those who may only have studied the rather misleading accounts of hypopituitarism which were current in medical textbooks a few years ago, three points must be made clear. Firstly, the patient's nutrition is usually quite satisfactory. A significant degre of emaciation throws serious doubts on the diagnosis of hypopituitarism, though it does not necessarily disprove it. Secondly, though no woman looks her best when she is in coma, these patients do not show premature senility. Thirdly, the state of the teeth is quite irrelevant.

When it has been established that the patient has a severe hypopituitarism, it may be accepted as reasonably certain that a coma of the type described here is due to the endocrine disturbance. Nevertheless, the other cause of coma should, of course, be excluded so far as is possible. In addition, if pathological facilities are available, a sample of blood should be collected for estimation of the blood sugar and any other examinations which may appear advisable.

If the existence of the hypopituitarism is not recognized, the coma may be incorrectly attributed to other conditions: (*a*) cerebral thrombosis, because of the gradual onset; (*b*) epilepsy, because of the convulsions which sometimes precede the coma; (*c*) meningitis, because of the rigidity of the neck; (*d*) uraemia, because of the white and sometimes puffy face and perhaps because of pyuria which may be mistaken for albuminuria; however, the blood pressure is not raised; (*e*) myxoedema, because of the appearance of the face, the dry skin, and the history of mental dullness and physical weakness; or (*f*) narcotic poisoning.

Types of Coma

In most cases hypopituitary coma seems at first sight to be of a rather uniform pattern. However, there are in fact

several different clinical and biochemical varieties. These variations are as yet not clearly understood, but certain broad clinical types can be recognized.

(1) *Pyrexial.*—The temperature is high (about 102 to 105° F.—38.9 to 40.6° C.), but the pulse rate is not correspondingly fast. The blood pressure is low (systolic pressure about 80). The coma is usually of gradual onset and tends to be of spastic type.

(2) *Hypothermic.*—In this group the coma is also of gradual onset in most cases but is commonly of flaccid type. There is no radial pulse and the heart is beating very feebly at a rate of about 30 to 40 a minute. The respirations are also very shallow and slow. The patient feels very cold to the touch. The temperature is usually recorded as 96 to 97° F. (35.6 to 36.1° C.), but this simply means that the clinical thermometer has failed to register. An ordinary chemical thermometer must be used to measure the true temperature. If the bulb is passed up the vagina to near the cervix, the stem protrudes far enough to allow a reading to be made without removing the thermometer. With this method it is found that the temperature is actually in the eighties or even in upper seventies (26–30° C.).

(3) *Hypoglycaemic.*—This is a general clinical group which includes cases which have a blood sugar of 15 to 30 mg. per 100 ml., and also a number of less typical cases with blood sugars as high as 50 mg. The temperature and pulse are about normal; the systolic blood pressure is about 100. In these cases the coma tends to develop rapidly, sometimes early in the morning. One variety is characterized by heavy sweating which often precedes the coma; these patients may recover consciousness quite suddenly and without treatment after a few hours of coma.

(4) *Other Types.*—The blood sugar is at a relatively normal level. The temperature and pulse are normal and the blood pressure is rather subnormal. The coma is commonly preceded by a few days of vomiting.

Treatment

There is as yet no specific treatment of the coma. Many of the patients recover spontaneously, and it is thus difficult to assess the value of any particular line of therapy. Nevertheless in practice certain methods are undoubtedly useful.

Intravenous Glucose.—If the blood sugar is very low, and the coma has not lasted too long, the intravenous administration of glucose usually has a dramatic effect. There are other cases in which the blood sugar is not extremely low but in which intravenous glucose produces a rapid though sometimes only partial improvement. In other cases, particularly the pyrexial and the hypothermic types, this treatment seems to be useless. In practice, it is only rarely that the results of blood-sugar estimations are to hand before treatment has to be begun. Nevertheless it is worth while to give glucose as a "blind" routine treatment to all the patients, or at any rate to those whose temperatures are normal. A significant proportion of the cases are hypoglycaemic and will be cured by glucose, and the others will be made no worse. One precaution must, however, be observed. Within a couple of hours after giving a large dose of intravenous glucose to a patient with hypopituitary coma the blood sugar may fall again to levels of 30 mg. or less. It is therefore important that, when the glucose has been begun, it should be continued for many hours, and that a careful watch on the blood sugar should be maintained afterwards.

The best method of administration is by intravenous drip of 20% glucose solution. The first half-litre may be given quickly, but thereafter the solution should be given at a rate of 1 litre every 8 or 12 hours (about 20 or 30 drops a minute). If the emergency appears serious and no continuous drip apparatus is at hand at the time, the glucose solution may be injected intravenously with a syringe in a dose of 100 ml. every hour until the apparatus can be obtained. In such a case it is wisest to cut down on a vein at the ankle and insert a fine "polythene" tube which can be left in place for a day; it is essential not to ruin all the available subcutaneous veins, because these will probably be required on many occasions later.

Treatment of Hypothermia.—The second line of treatment is that of patients in severe hypothermia. In these cases it is very difficult to raise the body temperature with hot-water bottles, and it is correspondingly easy to burn the skin. The most satisfactory method of warming the patient is to put her into a tepid bath (about 95° F.—35° C.) and gradually add hot water to it until a pleasant hot-bath temperature (about 102° F.—38.9° C.) is reached. After the patient has been in the hot bath for about half an hour, her heart rate increases gradually, the pulse returns at the wrist, and the temperature in the mouth begins to rise. It takes about two hours to bring the heart rate and temperature to normal levels. At this stage the patient usually shows signs of returning consciousness. She is lifted out of the bath, dried quickly, and placed in a warm bed. If the treatment is successful, she recovers full consciousness in the course of the next day.

Antibiotics.—Patients with pyrexial coma are usually given antibiotics, and sometimes recover from the coma after the temperature has settled. In other cases without pyrexia, the same therapy may be given with the object of preventing the subsequent development of a pneumonia, just as in any other comatose patient. The treatment is non-specific, so the choice of antibiotic is a matter only of personal preference, with the proviso that the administration must be either intramuscular or intravenous.

Hormones.—Finally, consideration must be given to the use of various hormones in the treatment of the coma. The patient is suffering not only from a total insufficiency of the anterior pituitary, but also from an extremely severe insufficiency of the adrenal cortex and of the thyroid. There is thus a very strong theoretical argument for giving adrenocortical and thyroid hormones. In practice, however, these treatments are disappointing. Cortisone, "eucortone," deoxycortone and salt, and testosterone have usually been given. Some of the patients have recovered gradually in the course of a day or two; others have died. There is no convincing evidence that these treatments changed the course of the coma from what it would have been if no treatment had been given. On the other hand, there is no evidence that cortisone is harmful in these cases, and thus there is no particular reason for withholding it if the doctor believes that it may do good. The usual dose is about 100 mg. intramuscularly each day; successes and failures have been claimed with doses ranging from 25 to 700 mg.

General Prophylaxis

After the patient has recovered from the coma it is as well to refer her to hospital for a full endocrinological study, which may take a few weeks. She will probably return home on a maintenance dose of 12.5 mg. of cortisone daily, usually with small amounts of thyroid and testosterone in addition. It is essential to continue this cortisone therapy permanently, not only because of its effect on the general health of the patient but also for two other reasons. Firstly, there is increasing evidence which suggests that continued treatment with cortisone prevents recurrences of coma. Secondly, it is possible that the sudden withdrawal of treatment may lead to an attack of coma a few weeks later.

Apart from this mainstay of treatment, care must be taken to avoid the following factors, which are known to precipitate coma in these patients.

1. General anaesthetics, even for minor operations. If anaesthesia is essential a preliminary boosting dose of 50 to 100 mg. of cortisone is usually advised on theoretical grounds, though, in the nature of things, it is difficult to get any real proof that this treatment is of practical value.

2. Morphine, barbiturates, and many of the other sedatives. The usual reason for giving these drugs is as premedication before operations under general or local

anaesthesia, or to control a patient during one of the attacks of mental disturbance which may occur in hypopituitarism. Drugs of this type are best avoided.

3. Insulin is very dangerous to these patients and should never be given to them except for certain special laboratory tests.

4. If the patient does not have adequate nourishment for a day or two she may become comatose. Feeding should be continued throughout any illnesses.

5. Even apparently minor illnesses may lead to coma and should be treated at their onset. Attacks of diarrhoea and vomiting are dangerous. Many lung conditions such as pneumonia, gangrene, or tuberculosis can be astonishingly symptomless in the patient with hypopituitarism, and their only obvious clinical effect may be to produce coma.

6. It is stated in many textbooks that the administration of thyroid is very apt to produce coma in patients with hypopituitarism. There is no real evidence to support this idea, and in fact a dose of 2 gr. (0.13 g.) of thyroid daily is usually quite harmless. However, some patients do appear unduly sensitive, and others who have been misdiagnosed as myxoedema are treated with steadily increasing dosage of thyroid until vomiting and diarrhoea are produced. Such alimentary tract disturbances are of course serious.

7. These patients are unable to produce a diuresis, and excessive fluid intake may thus lead to water retention though with no overt oedema. Recent observations suggest that this sometimes gives rise to coma.

Next article on Emergencies in General Practice.—"Home Care of Premature Children," by Dr. F. J. W. Miller.

Refresher Course Book.—Copies of the second volume of collected articles from the Refresher Course for General Practitioners are still available at 25s. (postage 1s.) each. The first volume is now sold out.

Clinical Pathology Book.—"Clinical Pathology in General Practice," a collection of 39 articles on clinical pathology that appeared in the *Journal* as part of the Refresher Course for General Practitioners, is now available, price 21s. (postage 9d.).

Both these volumes are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller.

CONTRIVANCE OF COLLEGIATION

HARVEIAN ORATION

The 236th Harveian Oration before the Royal College of Physicians of London was delivered on October 18 by Sir John Charles, Chief Medical Officer of the Ministry of Health.

In his introduction the Orator described briefly what was known of Harvey and his work and his services to the College. Much of his material had been culled from Harvey's *Praelectiones*, which he regarded as having been too little studied. It illuminated Harvey's rich fund of general knowledge and the philosophic bent of his mind. Of the ancient authorities on medicine Aristotle was to Harvey the prince of philosophers, and, like Harvey, Aristotle was a member of the household of a king. The father of Aristotle, Nicomachus, was court physician and friend of Amyntas II, father of Philip of Macedon and grandfather of Alexander the Great, and his son Aristotle was thought to have followed for a time his father's calling of physician. Later Aristotle became the tutor of the young Alexander, instructing him, among other accomplishments, in the use of drugs.

The Orator passed in review other court physicians: Grimbald, the physician of Henry I, whose claim to immortality was that he occasionally witnessed official papers, and John Francis of St. Albans, the surgeon of Edward I, who appeared in the Treasury accounts as something of an over-prescriber of drugs. But it was not until Thomas Linacre came on the scene that a court physician was found who was able to influence the royal mind for the benefit of the profession in general. "It is difficult," said the Orator, "to escape from the conclusion that this was the influence which determined the first Medical Act of 1511 which separated out the 'cunning' physician from the 'uncunning' practitioner of sorcery and witchcraft and recognized his status." Moreover, it was due to Linacre's genius that the Royal College of Physicians was founded, thereby bringing the "contrivance of collegiation" into play for the protection and furtherance of the interests of the profession as a whole.

Though Harvey was in attendance at the courts of James I and Charles I and was indeed a trusted servant of the latter, he was employed less as a physician than as an emissary, and even as an emissary his influence on royal policy was negligible. Of even less political influence was his colleague Turquet de Mayerne, chief physician to James I, who became a Fellow of the College by invitation in 1616, and, while never actively participating in its work, was always willing to use his good offices in its service. Mayerne was a man of great medical reputation and considerable financial ability. He had intimate contact with the courts of France and England; yet, like Harvey, his influence on the policy of the rulers he so assiduously courted was quite negligible, and there was no record that he inspired any Government action even when it concerned the health of the nation.

Growing Prestige of the College

In marked contrast to the ineffectiveness of these medical intimates of rulers throughout the ages was the history of the College in the evolution of its functions, the assumption of responsibilities, and the acquisition of prestige. The Orator went on to describe how the College concerned itself primarily with the qualifications of those who were seeking its licence to practise, often in defiance of influential persons whose recommendations had been given to the unworthy; how it evolved the vestiges of a medical curriculum in the advice given to unsuccessful candidates that they should take a four-year course of Galen, with the set books all carefully listed; how it examined and adjudicated on the standards of practice of Fellows on the receipt of complaints; and how it became responsible for the inspection of grocers and apothecaries, who were enjoined to display their ingredients "in the windows of their shops, so that physicians passing by might judge of their goodness." Among other acts of general application the College compiled the first pharmacopoeia in this country—the *Pharmacopoea Londinensis*.

Spirituous Liquors

The Orator went on to give examples illustrating the virtues of the contrivance of collegiation and of the strength which close and friendly collaboration could confer on professional men who, individually, even in what might be regarded as most favourable circumstances, could exercise little effect on conditions affecting their own profession and the welfare of the people committed to their charge.

The enormous and devastating growth of the consumption of spirituous liquors, especially gin, in the early eighteenth century became a national scandal. In 1725-6 the College took the initiative by offering to the House of Commons in January certain representations against the pernicious use of such liquors. In these representations it was stated that it was the duty of the College to take care of the health of His Majesty's subjects in London and within a seven-mile circuit, and that it had for some years observed with concern the fatal effects of the consumption of several sorts of distilled spirits upon great numbers of both sexes. Despite the fact that it took thirty more years of hard campaigning by humanitarian persons to goad the

Government into remedial action, credit must go to the College for having initiated the reform at a time when vested interest was most powerfully on the side of the distillers. But the College had never confined itself to administration of academic matters. In times of pestilence its members were to be found at the bedside of patients in the foci of infection. In 1558 the election of Caius to the presidency had been deferred "because all the Fellows were in various parts of the City giving help to the people suffering from tertian fever, which had increased among the inhabitants during the months of August and September. During those months there were hardly any healthy people to look after the sick, and hardly any reapers who could bring in the harvest."

In 1630 and again in 1637 the College was brought into consultation by their lordships of the Privy Council. The later inquiry resulted in the College submitting to their lordships a long and detailed summary of the annoyances likely to increase the sickness of the citizens of London. The document ended with the suggestion that a Commission or Office of Health might be set up to regulate these matters.

After reciting other examples, Sir John Charles concluded as follows:

"Through the mouth of his Orator William Harvey communicates annually his message to the Fellows and Members of this College, enjoining upon them the commemoration of all benefactors, the pursuit of knowledge, and the fostering of mutual love and affection—an *Aes triplex* of commendation. All these desirable things are within the compass of our Collegiation, all are of the essential needs of our age and calling. All, in the words of Harvey, are a string tying us to eternity."

CONFERENCE ON CEREBRAL PALSY

A conference on cerebral palsy, the present position and future possibilities, arranged by the British Council for the Welfare of Spastics, was held in the Great Hall of B.M.A. House, London, on October 13, when the chair was taken by Dr. J. A. SCOTT, Medical Officer of Health and School Medical Officer to the L.C.C.

Mr. D. F. VOSPER, M.P., Parliamentary Secretary, Ministry of Education, in opening the conference, said that the problem of the handicapped child offered an opportunity for partnership between the State and voluntary organizations. It must be borne in mind that there were many categories of handicapped children, and the 1944 Act in many ways revolutionized the approach of the State and local authorities towards all of them, but in the last few years the spastic child had received more attention than any other in the handicapped field. Yet cerebral palsy accounted for only about one-fourth of the handicapped children who required special education. This perspective must not be lost.

The parents of the spastic child had been given renewed hope, but it was important that the public should not exaggerate the limited amount which could be done to-day. It would be a false kindness to suggest to parents that all children, even with the best care, could be completely rehabilitated. A proportion of spastic children would not be able to benefit educationally, however much care was given.

Scope and Limitations of Treatment

Professor N. B. CAPON, Professor of Child Health, Liverpool University, spoke on the scope and limitations of the treatment of cerebral palsy, restricting his remarks to the nervous sequelae of the primary affection. The effectiveness of treatment depended mainly upon the patient's co-operation. He had to be trained to treat himself. He had to learn to perform certain movements, how to relax spasm and how to co-ordinate muscular actions, and, if appropriate treatment was available to him, his success would depend more upon his intellectual status than upon any other factor. He had to understand what he was trying to do, and he must take an interest in his own progress. This was not to say that a mentally retarded spastic was beyond help, but they could not feel satisfied with the results of their present treatments except in the relatively small percentage of spastics whose intelligence was at least equal to that of the average normal child. It was indeed a great advance when people began to realize that a spastic's intelligence, and therefore his prospects of deriving help from treatment, were often less impaired than his appearance suggested.

In a brief and simplified form Professor Capon put forward his suggestions for the treatment of spastic patients as follows. In each district of over, say, 50,000 people there should be at least one doctor who, without restricting his practice to cerebral palsy, was interested in it and had had experience in its diagnosis and treatment. He should be consulted as soon as possible about suspected cases. Each patient had to be considered as a family problem as well as an individual sufferer, and no two family problems were alike. The grouping together of patients suffering from the same chronic disability was usually undesirable, especially in childhood, though it might sometimes be necessary for administrative reasons connected with special treatments. The aim should be to ensure that, whenever possible, the handicapped child should have the benefit of adequate contacts with normal children. Similarly those who gave special treatments to spastic children should also be employed, whenever possible, in treating other types of disability.

After Professor Capon's address a discussion, opened by Dr. MARJORIE WILSON, of the Ministry of Education, was held on the placement of cerebral-palsied children, in which a number of directors of education, headmasters and headmistresses, and social-welfare and youth employment officers took part.

CIBA FOUNDATION DISCUSSION

LUMBAR DISK LESIONS

The sixth of a series of informal discussions on clinical problems of topical interest, planned with the co-operation of Dr. BASIL KIERNANDER, was held at the Ciba Foundation on September 26. The chairman was Professor J. TRUETA, and the subject "The Treatment of Lesions of the Lumbar Intervertebral Disks."

Mr. JOHN CHARNLEY, the opening speaker, discussed, and showed a film to illustrate, his recent research on the use of the straight-leg-raising sign in the management of sciatica. In 20 cadavers he measured the amount of movement of the fifth lumbar nerve root during straight-leg raising. The average range of movement was between 2 and 8 mm.; an interesting and almost constant feature was that the movement occurred suddenly during the middle 30° of elevation. He considered this a most important sign: a positive finding was of both diagnostic and prognostic value, since he believed that a positive straight-leg-raising test indicated that operation might be expected to relieve the patient's sciatic pain. He emphasized that he was talking of pain produced during straight-leg raising on one side only. Moreover, the pain should be produced at less than 45° of elevation, and it should be possible to elicit it repeatedly with the pain occurring at the same angle of elevation each time.

Manipulation

Dr. JAMES CYRIAX spoke on the conservative treatment of lesions of the lumbar intervertebral disk, emphasizing that he did not share the usual views which were held on this subject. Conservative management, he believed, should be founded on three forms of treatment: (1) manipulation; (2) spinal traction; and (3) epidural local anaesthesia. The

choice of method depended on the results of a full clinical examination rather than on the *x*-ray findings. He did not decide beforehand which manipulation he would use, but was guided throughout the procedure by his patient's reactions. For this reason he did not believe in manipulation under general anaesthesia. In general practice probably 90% of the cases of backache seen were suitable for manipulation, but in the selected group appearing at his clinic at St. Thomas's Hospital only 50% were found to be suitable. Later, in answer to a question by Professor TRUETA, Dr. CYRIAX said that he had experienced no alarming complications attributable to his manipulations in the course of a very large series. When manipulation failed or was contraindicated, the application of spinal traction, or epidural local anaesthesia, were possible alternatives.

The orthopaedic treatment of prolapse of the intervertebral disk was discussed by Mr. P. H. NEWMAN. It was important to appreciate how varied was the clinical experience of all those who were called upon to treat this symptom. In one heavy industry the incidence of backache was 3% of the working population. Of these only 10% required to be referred for an orthopaedic opinion. Out of the total of 5,500 patients who attended this industrial clinic with backache only 5 needed to be referred for an operation. He felt that the major problem was the diagnosis and treatment of the more vague and ill-defined syndromes which one found in patients with backache, and not that of the clear-cut severe disk protrusion with sciatic pain.

Turning to orthopaedic treatment, he described manipulation as being a successful and excellent method, but the success was not due, as Dr. Cyriax suggested, to the replacement of the extruded disk. During the last year at the Royal National Orthopaedic Hospital four main diagnoses were reached in 316 patients attending on account of backache: low lumbar strain 92; chronic instability 84; prolapsed intervertebral disk (P.I.D.) 85; degenerative changes 55. His impression was that time and bed rest helped these patients with strain and P.I.D. Local injections were of value in cases of lumbar strain, while exercises helped all but the elderly patient with degenerative changes and those with acute P.I.D. Supporting corsets were of definite value in the aged, whereas manipulation had a place in all groups except the aged. He emphasized the importance of taking time to advise the patient fully about his condition.

Surgical Treatment

Mr. J. R. ARMSTRONG, whose topic was the surgical treatment of disk lesions, said it is essential to remember the progressive nature of disk lesions, with the possibility that the clinical picture might alter during quite a short time. He divided the potential process into three stages: the degenerative stage; rupture of the annulus; and the stage of healing. Immediate operation was important when there were cauda equina lesions with disturbance of bladder and rectal function. The prognosis in these cases was not good unless operation was undertaken immediately paralysis appeared. Late operations when there had been gross interference with nerve roots could not be expected to improve the paralysis.

A third indication for surgery was failure of conservative treatment, but much depended upon the views of the surgeons and the demands of the patient. These cases might be grouped as (1) cases with persisting severe pain; (2) cases of recurrent attacks each of which responded to conservative treatment; and (3) cases with an irritable lesion of the intervertebral joints. In his opinion operation was indicated in between 2% and 3% of proved cases of disk lesions and in something like 0.5% of all cases of backache.

A free exchange of questions and answers followed. The CHAIRMAN, summing up, was surprised at the measure of basic agreement discovered. He felt encouraged to give manipulation a trial; disappointed that no real contribution towards solving the difficulties in diagnosis had appeared; and pleased that the role of surgery seemed to be confined to such a small proportion of cases.

THE MOTOR SHOW

[FROM A SPECIAL CORRESPONDENT]

At this year's Motor Show 187 British cars and 100 competitors from six overseas countries—including Czechoslovakia—are on the stands, not to mention some 480 exhibitors of accessories and the multitude of components essential to the trade. Some half-million people will have gone through the turnstiles by the time the doors close on October 29. The prospective customer, having overcome some wishful thinking about a nice model at £7,502 (purchase tax included), will find much potentially good motoring at more moderate prices.

The manufacturers of the various standard cars have, on the whole, resisted the temptation to plaster their products with useless, but not rustless, chromium. The tendency has been to concentrate on those things which really matter to the driver who spends a great deal of time behind the wheel and expects to be comfortable. The cars on show are exactly the same as those which will be delivered against orders, but many buyers with recollections of past experiences will wonder if their cars will have had quite the same amount of careful examination as these exhibition models. There are too many stories of windows not fitting properly, doors out of alignment, and even certain things missing, things perhaps not vital but a cause of extreme irritation to the busy man—and particularly to the busy doctor—who can ill spare the time taken to put them right. An interview with a representative of the makers of one of a big manufacturing group of cars indicated that they were not unaware of these criticisms. Full production and a scarcity of skilled workers had apparently strained the normal organization to its limits. However, a satisfactory reassurance was given that inspection is to be improved in future and that so far as the things that mattered were concerned—that is, the mechanical part of the job—it had never been below standard.

Safety

With increasing emphasis on high performance, even in moderately priced cars, it is good to see that greater attention is being paid to safety. Some examples of this are not yet standard fittings, however, and are to be seen only on the stands for accessories. There is a safety belt and harness for drivers and passengers, and safety locks and a children's safety catch for rear doors. There is also a simplified device for aligning headlamps which, it is claimed, enables those with no specialized knowledge to make an accurate adjustment. Progress has been made on the disk brake, although the ordinary motorist must wait for the results of this progress; but conventional braking systems have also been improved. One noticed an increasing number of the wrap-round type of rear window which abolishes blind spots, and improved screen-wipers and washers. Tubeless tyres are already fitted on many models and look like becoming standard on all cars. Their slow deflating properties after puncture should lead to greater safety, and they are said to be easy to mend. Rear lights of enormous proportions featured on many cars, and one was reminded of a recent letter in the *Journal*, which pointed out their potential danger to the colour-blind. A "magnetic snake" for recovering small metal parts from inaccessible places is one happy little invention among other gadgets for the home mechanic.

The Rockefeller Foundation Appropriations for 1954 totalled $19,107,665, President DEAN RUSK announced on September 30, in his review of the year's work. Of this figure $5,102,796 was allotted to medicine and public health. A follow-up of the 190 Foundation Fellows of 1939 showed that, 15 years later, 76 had become presidents, deans, and professors in educational institutions, 45 were administrators and research workers in government units, and 29 were working in private hospitals and privately controlled non-profit institutions.

Correspondence

Carcinogen in Coal-tar

SIR,—In his letter (*Journal*, October 15, p. 969) under this title Dr. C. E. Goldsborough raises many interesting questions upon which some comment may be made.

(1) A large amount of attention has been directed already to the diesel engine as a source of carcinogens since the first observations in this laboratory by R. E. Waller[1] to which Dr. Goldsborough refers. Recently J. M. Campbell (unpublished observations) here has again detected 3:4-benzpyrene, and also several other hydrocarbons, in condensate from the exhaust of a diesel engine, and R. L. Cooper[2] began a study of the ratio of pyrene to 3:4-benzpyrene in this and other materials. Dr. Paul Kotin, of Los Angeles, and his fellow-workers have demonstrated upon mice the carcinogenic power of diesel products.[3]

(2) Dr. Goldsborough says, "... There would be two factors in the production of cancer of the lung: (1) concentration of carcinogen and (2) period of contact." A third factor which is at least as important is that of size of particles, and on this matter our knowledge is still very scanty. In a recent paper from the pathological laboratory, St. Bartholomew's Hospital,[4] data from the literature upon the relation between size of particle and depth of penetration into the respiratory tract were collected. Something like 80% of particles of diameter more than 2.5 μ are arrested in the nose; smokers facilitate the entry of particles into the lung by by-passing this filter. No comparisons of different sources of carcinogens—for example, town smoke and tobacco smoke—are of any value unless these factors, particle-size and nasal filtration, are considered. This problem appears in the section "Combined Intake of Benzpyrene from Air and Smoking" in the paper "Lung Cancer Death Rates among Non-smokers and Pipe and Cigarette Smokers," by Dr. Percy Stocks and Mr. John M. Campbell (*Journal*, October 15, p. 923).

(3) Dr. Goldsborough says, "... There is no doubt at all that the curve of deaths from carcinoma of the lung follows a little later, but closely parallel with, the curve of vehicle density of diesel lorries." All such arguments require a knowledge of the incubation period of cancer in man which we do not possess.

(4) The formation of methyl cholanthrene is not known to occur except in the synthesis of this compound in the laboratory.

Probably in a few years' time valuable information will come to us from the Scandinavian countries. Thus in Finland the use of the diesel engine is just beginning, and from 1953 onwards every case of cancer has been registered.—I am, etc.,

Department of Pathology,
St. Bartholomew's Hospital,
London, E.C.1.

E. L. KENNAWAY.

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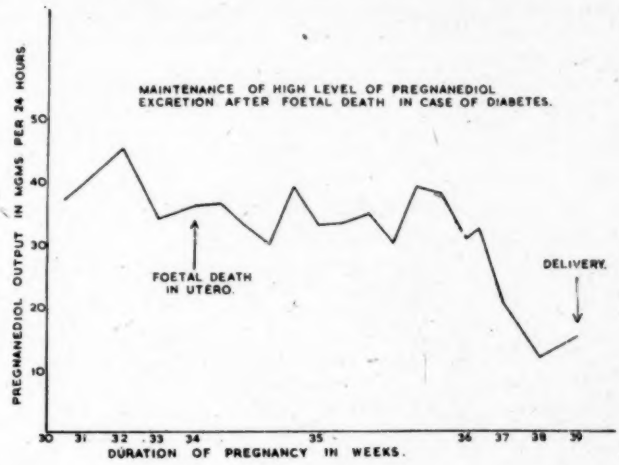
Management of the Pregnant Diabetic

SIR,—Mr. J. H. Peel (*Journal*, October 8, p. 870) has given us a very full account of the management of the pregnant diabetic. In particular we were interested in his preliminary report of the results of careful hormonal assays in these cases and in his suggestion that an "abrupt and progressive drop in the excretion of pregnanediol" indicates that perinatal death is impending. While this may sometimes be true, there is another side of the picture. Using the method of Klopper, Michie, and Brown[1] for pregnanediol estimation, which we have found to be a more accurate method of assay than those generally used, we have found normal values in association with foetal death in diabetic patients. For example, in four such patients in whom intrauterine death of the foetus occurred, repeated pregnanediol assays have shown normal levels of pregnanediol excretion, not only before foetal death but also maintained for some time, in one case for eleven days, after the death of the foetus. The details of one of these cases were reported at the British Congress of Obstetrics and Gynaecology this year.

Our experience is that in the pregnant diabetic a normal level of pregnanediol excretion is no guarantee that the


MAINTENANCE OF HIGH LEVEL OF PREGNANEDIOL EXCRETION AFTER FOETAL DEATH IN CASE OF DIABETES.
PREGNANEDIOL OUTPUT IN MGMS PER 24 HOURS
50
40
30
20
10
FOETAL DEATH IN UTERO.
DELIVERY.
30 31 32 33 34 35 36 37 38 39
DURATION OF PREGNANCY IN WEEKS.

foetus is not in danger. The difference between our opinion and that of Mr. Peel and his team may originate from differences in the method of pregnanediol assay. Mr. Peel does not give his methods but states that he estimates "pregnanediol and allied chemical compounds." The method used by us has been found to give a specific assay of pregnanediol. We have already shown that many of the older methods are so inaccurate as to justify the opinion that they should be discarded for routine use[2]: the method of Klopper *et al.* is much more accurate, and should be preferred.—We are, etc.,

MARY G. COYLE.
F. L. MITCHELL.
C. S. RUSSELL.

Sheffield.

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Food-poisoning

SIR,—Dr. P. Mestitz (*Journal*, October 1, p. 854) points out the potential danger of the handles of water closets. I have always endeavoured to avoid this enteritic pitfall by (1) using the left hand to pull the chain; (2) grasping the chain itself and not the handle when using public lavatories; (3) opening the lavatory door with the left hand on leaving.

The introduction of foot pedals would not eliminate the danger of the contaminated door handle.—I am, etc.,

H.M.S. Corunna. R. E. DREAPER.

Incompatibility of Aluminium Hydroxide and Certain Antibiotics

SIR,—Because digestive upsets often follow oral administration of the tetracycline family of antibiotics (chlortetracycline, oxytetracycline, and tetracycline), the practice has arisen of giving aluminium hydroxide as well. That this is an undesirable practice seems to follow from a quantitative study of the affinity of tetracyclines for various cations.[1]

The following model experiment has now been carried out using commonly prescribed doses: aluminium hydroxide gel *B.P.C.* (8 ml.) was added to chlortetracycline hydrochloride (0.25 g.) in water (250 ml.). From the *p*H (6.48) and from the data yielded by potentiometric titration in the presence of known concentrations of aluminium cations, we have

calculated that all of the drug was firmly bound to the aluminium hydroxide. Thus the reason for the abolition of digestive upsets becomes clear: the drug is no longer present. It is doubtful if it would be liberated to any extent during the passage of the aluminium complex along the intestinal tract, unless highly acidic conditions—e.g., *p*H 2—obtain in the large bowel, which is unlikely. The other tetracyclines behave similarly, and it would seem that milk (commonly given for this purpose in U.S.A.) should replace aluminium preparations as a protective agent for the gastro-intestinal tract, when these antibiotics are administered.

We trust that this information is of value to your readers.—We are, etc.,

ADRIEN ALBERT.
CHARLES REES.
London, N.W.1.

REFERENCE

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Tuberculosis of the Pubis

SIR,—The report in the *Journal* (October 1, p. 832) by Mr. P. Gilroy Bevan of a case of tuberculosis of the pubis prompts me to refer briefly to two cases of this rare condition I met with many years ago.

In 1909 a boy aged 11 years was brought to hospital with a sinus in the left ischio-rectal region. Radiographs showed what I regarded as a tubercular focus in the left pubis. Radical operation was followed by a completely satisfactory result: this lad did very well in the Army in the first world war. In 1912 his brother, aged 11½, was seen with a cold abscess in the adductor muscles of the right thigh, the site of the abscess in Dr. Bevan's case. Radiographs showed, in the right pubis, a focus of disease similar to that seen in his brother. The case was treated by aspiration, with a satisfactory result.

The diagnosis in these two lads was never in doubt, but unfortunately in neither was the type of infection actually proved. The fact that in these two brothers the disease occurred in the same bone, and that an uncommon site for tubercular infection, is remarkable.—I am, etc.,

London, N.W.1. H. A. THOMAS FAIRBANK.

Paediatrics

SIR,—Paediatrics, as I was taught it, began with the assumption that the child is but a miniature version of the adult. We were led tacitly to assume that his diseases, apart from exanthemata, were the same as in adults but less severe; that his psychological make-up was similar to that of the adult but more innocent; and that his treatment is identical except that it is scaled down to size by Clark's rule. No mention was made of the important differences that exist between the growing child and the adult who has already stopped growing. Nor was mention made of the special problems that arise out of these differences, particularly with regard to normal and abnormal blood values, prenatal and post-natal physiology, orthopaedic and surgical therapy, cardiology, gastro-enterology, and even paediatric gynaecology. In short, I left medical school with the belief that paediatrics was the study of infant feeding.

It seems to me that we start our medical studies the wrong way round. We begin with the finished product—i.e., the adult—but pay scant attention to the raw material from which he develops. If I may state the obvious, Sir, a child is *not* an adult, and the study of children covers every specialty in medicine except the newest—namely, geriatrics. In addition it requires special training and experience to handle infants and children, to understand their problems, and to treat them. What makes paediatrics unique is the additional complication in the form of parents who require a special approach.

In order to overcome these difficulties, therefore, we need a medical school that is "paediatrically orientated." Rather than burden the already overburdened student by lengthening the child health course, a medical school should be established which is devoted to the study of the child in health and disease. Adult medicine would take second place and its study would be in logical sequence. The end-result would be paediatric G.P.s who would devote themselves to children and give them the full benefits that medical science has to offer.

It requires a bold imagination to encompass this scheme, but it is just this characteristic which has made it possible for the British people to lead the world in social experiment.—I am, etc.,

London, S.W.4. PINCUS CATZEL.

Poliomyelitis Simulating Tetanus

SIR,—I was most interested to read Dr. Stella Manners's case report of poliomyelitis simulating tetanus (*Journal*, July 2, p. 27), and would like to draw a comparison with a recent admission here.

A boy of 2½ years was admitted to a cubicle in our children's ward three weeks ago with a history of increasing stiffness of legs and back for two days. On admission he showed board-like stiffness of back, neck, and legs, and a generalized muscle jerking resembling tetany. His cerebrospinal fluid showed 88 cells, 80% lymphocytes, protein 30, chlorides 670, sugar 86. It was felt that poliomyelitis was the most likely diagnosis and he was transferred to an isolation hospital. At the isolation hospital it was felt that his muscle spasm was so much like tetany that he was treated with calcium gluconate. This treatment appeared to produce initial improvement, but his course was downhill, and he died three days after his original admission. At necropsy there was congestion of the pia arachnoid over the brain and spinal cord. Histology showed widespread lesions of anterior poliomyelitis in the cord, and to a lesser extent of the brain stem.

The cerebrospinal findings and history in this case fitted the diagnosis of poliomyelitis. An opinion has been expressed suggesting that the tetanic element was latent and that it was shown up by the severe infection.—I am, etc.,

Luton. DERIC B. HAWKINS.

Phenoxymethyl Penicillin

SIR,—The advantages of oral over parenteral therapy need no emphasis, especially in paediatric and general practice, so I was glad to take the opportunity recently afforded me to try a new form of oral penicillin for which a high degree of reliability is claimed. This is phenoxymethyl penicillin, a pure acid, which unlike other types of the antibiotic is resistant to acid. Spitzy[1,2] and Hausmann and Zischinsky,[3] among others, have reported clinical success with it, but so far nothing has appeared in British journals. Although the numbers of this trial are few, the results confirmed the Continental reports, and were so satisfactory that they seemed to justify a preliminary note. Further work is in progress.

The adult patients were given 1 tablet of 60 mg. four-hourly and before meals; children received half a tablet similarly. To avoid interrupting sleep the last dose at night was doubled. In brief the cases were as follows: *Puerperal mastitis:* Two patients; condition subsided well in 36 hours. *Boils in the nose:* Five cases, all cleared up quickly. *Septic finger:* One of these two closed infections was cured soon, the other failed to respond. *Tonsillitis:* Eight children all did well and cleared up in 36 hours; the response here seemed particularly good. *Otitis media:* The temperature in all five children was down to normal in 48 hours, and they were all cleared up in 96 hours. *Measles prophylaxis:* Ten children; no complications developed in any, and all had a straightforward convalescence. *Erysipelas:* This patient required intensive therapy, and 500,000 units crystalline penicillin was injected every morning and phenoxymethyl penicillin given for the rest of the day as with the others; he made an excellent recovery in five days. *Bronchopneumonia:* Two elderly women patients (aged 78 and 75) did not respond satisfactorily to 1 tablet 4-hourly, but recovered when parenteral penicillin was given. It is possible that intestinal absorption in the elderly may not be so efficient and a larger dose may be required.

In conclusion it should be said that these preliminary observations of phenoxymethyl penicillin (to which the name "distaquaine V" is also applied) were made under the ordinary conditions, limitations—and advantages—of general practice.—I am, etc.,

Sutton, Surrey. A. G. BOWERBANK.

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Diagnostic Pneumoperitoneum

SIR,—I can endorse the opinion of Drs. S. C. Truelove and K. Lumsden (*Journal*, September 3, p. 585) on the value of pneumoperitoneum as a diagnostic aid. This method has been used successfully, and without ill effect, since 1951 in 78 cases at the Baragwanath Hospital.

Air has been introduced for the following reasons: (1) to show the position of the diaphragm and its relation to the shadow under investigation; (2) to indicate the cause of any deformity of the diaphragmatic contour, and in particular to distinguish a raised antero-medial leaf from the bulge produced by a pathological liver; (3) to demonstrate general or local adherence of the superior surface of the liver to the diaphragm. The procedure has been most helpful in cases of suspected hepatic amoebiasis presenting with right-sided pleural effusion or lung abscess; in amoebic abscess of the superior surface of the liver; and occasionally in primary hepatic carcinoma. It has been noteworthy how often a splenic shadow not visible on a plain film has been shown clearly after the introduction of air. Patterns revealed at this hospital, which serves a large African population, have been strikingly similar to those illustrated in the report by Clark and Dutta.[1]

The original idea of insufflation of air to provide a contrast medium is attributed to G. Kelling (1902) by Stewart and Stein.[2] The latter authors recommended that oxygen be used and that the prone position be employed in radiography of the upper abdomen.—I am, etc.,

Johannesburg. K. J. KEELEY.

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Sickness and Mortality Records

SIR,—In your annotation on "Sickness and Mortality Records" (*Journal*, September 17, p. 730) you refer to the Registrar-General's finding that the admission rate for alcoholism to mental hospitals in England and Wales in 1950 and 1951 was much greater for social class I (professional and administrative) than for any other class.[1] The *Statistical Review* states that, "whereas the proportions of males in classes I and II in the [1951] census population were 33 and 150 per 1,000 respectively, the proportion among admissions for . . . alcoholism [were] 154 and 259." According to the Registrar-General "this may indicate that alcoholics in these social classes pay more frequent visits to hospital than those in the other social classes, or it may indicate a higher incidence of alcoholism."[1]

In trying to find an answer which of these possibilities is the more likely one, it is advisable to keep in mind that American observers have frequently stressed the danger of generalizing from one particular group of alcoholics to "alcoholics" in general,[2,3] and that, for example, Amark[4] in Sweden found marked differences of social status between groups of alcoholics drawn from different sources. The occupational distribution among alcoholic males admitted to Warlingham Park Hospital in the period 1952–4 corresponds fairly closely to that of alcoholics in mental hospitals in England and Wales in 1950–1, the proportion for classes I and II being 17.2% and 34.5% respectively.[5] However, recent studies by Dr. Whiteley and myself have shown that among alcoholics and heavy drinkers in a reception centre 75% belonged to class V. On the other hand, Dr. J. J. Fleminger and I found that class III was most frequently represented in a sample of alcoholics admitted to an observation ward, amongst whom approximately one-third had "skilled occupations" (class III), a slightly smaller number had "unskilled occupations" (class V), and only one-quarter belonged to classes I and II. Alcoholics in observation ward, reception centre, and mental hospital differed also in many other aspects.

Thus alcoholics admitted to mental hospitals can apparently not be considered to be a representative sample of the total alcoholic population in this country. Their anomalous social distribution can therefore not be taken as showing a higher incidence of alcoholism among the upper social classes, but rather as indicating the likelihood of the other explanation that, for some reason or other, alcoholics in classes I and II "pay more frequent visits to hospital."—I am, etc.,

Warlingham, Surrey. M. M. GLATT.

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Contraindications to Thiopentone Anaesthesia

SIR,—Your leading article on "Contraindications to Thiopentone Anaesthesia" (*Journal*, October 1, p. 836) is at variance with our teaching in the department of anaesthesia at the Royal Victoria Infirmary.

One of the greatest hazards the patient can undergo is from the *rapid* administration of thiopentone. A full, or partly full, stomach is obviously a contraindication to the *slow* injection of the drug. Furthermore, it is to be doubted whether a full stomach can *certainly* be emptied "by means of a tube." I believe that thiopentone, and/or a relaxant, should never be administered to a patient who is likely to vomit before a cuffed endotracheal tube has been inserted.—I am, etc.,

Newcastle-upon-Tyne, 1. M. H. ARMSTRONG DAVISON.

Sacro-iliac Strain

SIR,—I strongly concur with Mr. T. T. Stamm on his views of sacro-iliac strain (*Journal*, October 1, p. 833), and it is a pity that this diagnosis has been submerged by the more popular disk lesion. The probable reason for the confusion is that the differential diagnosis is difficult. I offer two additional diagnostic pointers to the ones which he gave in differentiating sacro-iliac from lumbar joint strains. Sacro-iliac lesions cause increased tension in the sacro-tuberous ligament on the affected side; this tension is palpable and there is tenderness along the course of the ligament. Also there is usually unilateral erector spinae muscle guarding—this may be quite severe or merely slight, but it is almost invariably present, whereas in disk herniations there is always bilateral erector spinae muscle guarding, albeit asymmetrical at times.

Finally, there can be no doubt that specifically applied manipulations to the sacro-iliac joint are effective in relief of pain there. There are osteopathic manipulative techniques which will move the sacro-iliac joint and yet do not affect the lumbar joints. If such manipulations clear the pain, the source of the pain must have arisen in the sacro-iliac joint.—I am, etc.,

London, W.1. ALAN STODDARD.

SIR,—The article by Mr. T. T. Stamm (*Journal*, October 1, p. 833) will, I am sure, herald the return of sacro-iliac joint lesions to medical orthodoxy. Manipulative treatment of this joint, at the hands of bone-setters, football trainers, etc., has in the past relieved many patients of disabling symptoms, sometimes to the chagrin of their orthodox practitioners.

Mr. Stamm's article points out some of the features of sacro-iliac lesions, but not all of them. The main features which he does not seem to recognize are that the normal sacro-iliac is a mobile joint—reference to Gray's *Anatomy*[1] will soon convince any sceptic about this—and that the abnormal sacro-iliac joint is usually stiff. Bourdillon[2] describes the method of testing the sacro-iliac joint for mobility, and

mobility is best restored by following Bourdillon's instructions for manipulation of the lumbar spine, but the forward pressure should be localized to the posterior iliac spine.

Mr. Stamm's hope and belief that the condition is unknown in the elderly is unfounded. Recently I have treated an old lady of 70 years who has gross osteoarthritis of hips with ankylosis on one side and greatly diminished movement on the other. Her main complaint was of pain low in the back where "there is a bone out of place." The errant bone was the posterior superior iliac spine, which returned to normal prominence after manipulation. She required a second manipulation, which, as in Mr. Stamm's cases, was less dramatic than the first, but her low back pain has been relieved.—I am, etc.,

Banbridge, Co. Down. H. W. GALLAGHER.

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Efficacy of Current Cerumenolytics

SIR,—In his comparison of cerumenolytic agents (*Journal*, September 17, p. 722) Squadron-Leader R. Hinchcliffe found olive oil to have been the most effective and "cerumol" the least. This conclusion differs markedly from the impression that I have gained in general practice, and I cannot help wondering whether there was some defect in his method.

Where a hard wax plug is present I usually instruct the patient to instil cerumol drops for two or three days before I undertake the syringing. When this is inconvenient I instil five drops of cerumol into the ear, the patient keeping his head inclined for at least two or three minutes. I may then place a piece of cotton-wool in the pinna, but I do not plug the meatus as mentioned in the article, for the cotton-wool would absorb the cerumol. Twenty minutes later the ear is syringed, and I usually require between two and four fillings of the syringe. It is because this takes appreciably less than five minutes, and because I cannot recall any failures, that I question the findings in the above investigation.

The striking advantage afforded by cerumol as compared with other agents is that less pressure is required to dislodge the wax, and the patients therefore do not complain of discomfort afterwards. I feel sure this outweighs the mild burning sensation which cerumol sometimes evokes and which seems to have been less remarked upon by patients recently.—I am, etc.,

London, N.W.11. RICHARD I. RANDALL.

Anaemia in the Tropics

SIR,—In their letter (*Journal*, August 6, p. 376) Drs. Henry Foy, Athena Kondi, and B. Sarma say they have the impression that the diets of the tea garden workers in the area of their investigations did not appear to be faulty. I am sorry they did not do a critical survey of them, as I have the opposite impression for an area 50 miles away, on the opposite bank of the Brahmaputra.

The labour population of this area is by no means a homogeneous one. Originally it was recruited from districts in Bihar and Orissa. The feeding habits of the members of each group are not uniform. In each, many are vegetarians, the bulk of their diet being rice, with a little *dal*, vegetables, and spices. Most of them will eat fish, but it is fairly expensive and often in short supply. As their vegetables are cooked excessively, I wonder what their value is nutritively. In theory, too, they drink milk, but, as the yield from a cow on the north bank is absurd by English standards, the daily per capita consumption must be quite small. Others from the same district have no scruples about eating meat. Some, indeed, have no objections to beef. An appreciable number of workers manage to save quite remarkable sums from their pay. This tends to reduce the amount of money available for buying food. In one garden in the area there does seem to be an association between hoarding of money, anaemia, and malnutrition. The amount of money available for food (and, perhaps, the ability to consume food) must be reduced further, to an unknown degree, by the local enthusiasm for alcohol.

My only objective observation about the diets is the amount of money spent on feeding patients in the garden hospitals of the area. In several of these the cost per head per day is around 6 annas (6d.). The minimum daily consumption of rice per head is about a pound, which recently has been costing 4 annas. Thus, all the other items, which are said to include *dal*, vegetables, spices, milk and chicken, meat and fish, when available, is bought with 2 annas. I do not know how much is spent on hospital feeding in other tea districts of Assam.—I am, etc.,

Assam. J. E. L. PRICE.

Functional Uterine Bleeding

SIR,—In thanking Miss Gladys Hill for a most stimulating paper on this common disorder (*Journal*, October 1, p. 812), may I be permitted briefly to discuss the improvement that follows curettage of a hyperplastic endometrium and draw a conclusion?

I have been struck by the diminution in size of the uterus when the organ is palpated bimanually under anaesthesia before and after curettage in these patients. The more profuse the endometrial curettings, the more obvious is the diminution in size of the uterus; the greater the myometrial retraction, generally, the better is the immediate therapeutic response. It would seem to me that the malfunction of the myometrium is as important as that of the endometrium, and that *pari passu* with the endometrial and hormonal studies we must try and find a safe, non-cumulative oxytocic effective in the non-pregnant state.—I am, etc.,

Chelmsford. ANTHONY C. PEARSON.

Treatment of Varicose Ulcers

SIR,—I was interested in Dr. William J. Hickey's letter (*Journal*, October 8, p. 910). I agree with his statement that the number of treatments proposed for varicose ulcers are legion. Many of them, I agree, are tried and found to be unsatisfactory. Dr. Hickey is merely emphasizing the necessity for a bandaging technique for the treatment of varicose ulceration. There are many other adjuvant treatments which can be well adopted in association with the bandaging technique—for example, the secondary disinfection of the ulcer with an antibiotic (to be adopted with care), the insertion of silver dinaphthylmethane disulphonate in the ulcer, etc., but ultimately, as Mr. Dickson Wright has so frequently emphasized, and as I tried to show in a colour film that I made for the Annual B.M.A. Meeting here five years ago, bandaging is undoubtedly the important thing—and we are indebted to Dr. Hickey for again drawing attention to this matter.—I am, etc.,

Liverpool, 1. STUART MCAUSLAND.

Premenstrual Varicose Veins

SIR,—I had not intended to enter into the esoterics of endocrinology, but I am afraid that both Mr. W. G. Mills and Dr. J. S. Norell (*Journal*, September 17, p. 736) are in error in invoking "the customary" and "the usual" progesterone story as the cause of premenstrual varices.

Indeed, I find it difficult to understand how such an aetiology could ever have been canvassed—unless it is, as Mr. E. Robert Rees (*Journal*, October 1, p. 852) points out, that we have been "far too ready to accept this explanation for all such effects ever since the physiology of progestin became known." The plain facts of the matter are these: progesterone production commences at about the 15th day of the menstrual cycle, reaches its peak at the 21st–22nd day, and then tails off, ceasing entirely two or three days before the commencement of the flow.[1] Premenstrual varices on the other hand appear in the 48 hours prior to menstruation—the very time at which progesterone is notable for its absence.

I was most interested in Mr. Rees's reference to uterine tumours. As it happens, McLennan's paper,[2] which deserves

recognition as the most careful and meticulous contribution to this subject, notes that the femoral vein pressure increases in these cases in a manner entirely comparable to that in pregnancy.

To sum up. First, as progesterone is invalidated as the cause of premenstrual varices it seems illogical to suggest that pregnancy varices, which behave in a similar way to their menstrual counterparts, should be due to this hormone merely because it is coincidentally present. Secondly, the uterus does not increase markedly in size in the premenstrual phase, nor is it enlarged enough to press on the iliac vein at the time when pregnancy varices first show themselves, and this would appear to dispose of the direct pressure theory. We are left with the only common denominator in premenstrual and pregnancy varices—namely, the vast increase in internal iliac venous return which is no doubt associated with the opening up of uterine arteriovenous shunts.

The nearest *in vitro* test of proof we have at the moment lies in simulating the physical fluid conditions in the iliac veins with a glass ⅄ tube, suitably valved, and noting the build up of pressure in the lateral limb when the flow in the medial limb is increased. Perhaps this correspondence will pave the way to investigations *in vivo*.—I am, etc.,

London, W.1. STANLEY RIVLIN.

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Combined Immunization

SIR,—The article by Miss Mollie Barr *et al.* (*Journal*, September 10, p. 635) and the letter from Dr. Harry Binysh (*Journal*, October 1, p. 850) would tend to bring into disrepute the use of adsorbed triple antigen. I feel it is only fair to take into account the technique used in the paper under consideration. It has long been accepted that adsorbed antigens are irritant, and, if given subcutaneously, tend to cause sterile abscess formation, and it is for this reason that intramuscular injection is recommended. In a series of 200 infants each receiving three injections (600 injections in all) of an adsorbed triple antigen,[1] only one sterile abscess occurred, but in this series care was taken to ensure the intramuscular injection of the antigen.

If the adsorbed antigen should produce better antibody formation, its use by intramuscular route would surely be justified. That a satisfactory response can be obtained in the older infants with a suspended antigen has been shown. That early immunization is desirable is accepted by many. It remains to be proved that a satisfactory response can be produced by use of saline-suspended triple antigen in the very young infant. The dangers of adsorbed antigen must therefore be weighed against what may well be its subsequently determined usefulness. With regard to the danger of poliomyelitis following the use of an adsorbed antigen, is not the policy during an epidemic to suspend as far as possible any form of injection therapy for which there is no immediate indication?

I feel we should not be too hasty in discarding a useful prophylactic agent on the strength of reported complications which may have been caused by faulty technique.

Dr. Binysh raises the question of the usefulness of tetanus immunization and wonders "whether passive immunization is not a more satisfactory alternative for those at risk." If he is worried about the circulating antibodies, surely these can be produced by "booster injections" when the child is at risk if previous immunization has been carried out. By this means the risk of serum sickness is eliminated, and this of course is of greatest importance in the allergic child. I think it is fair to say that many cases of tetanus arise from injuries not thought sufficiently severe to warrant a visit to the doctor, and it is in these that the presence of some antibody may make considerable difference to the prognosis.—I am, etc.,

Manchester, 13. G. V. FELDMAN.

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Obituary

J. M. BEATTIE, M.D., D.Sc.

We record with regret the death on October 10 of Professor J. M. Beattie, emeritus professor of bacteriology in the University of Liverpool, at his home at Formby, near Liverpool. He was 87 years of age.

James Martin Beattie was born in New Zealand on May 31, 1868, the son of Mr. William Beattie, of Alexandra, and was educated at the Arthur Sheet and Normal School, Dunedin, and at the University of Otago, where he graduated M.A., with first-class honours, in 1889. He was the senior scholar in natural history of the University of New Zealand. From Dunedin he entered Edinburgh University as a medical student, and took the degrees of M.B., C.M., with first-class honours, in 1894. In 1901 he proceeded to the M.D., receiving a gold medal for his thesis.

From 1901 to 1907 he held the post of senior assistant to the professor of pathology and lecturer in pathological bacteriology at Edinburgh, and for some of that time he was assistant pathologist at the Edinburgh Royal Infirmary. During these years he published several papers on the bacteriology of rheumatic fever and began the collaboration with the late Dr. W. E. Carnegie Dickson which led to their book on pathology. The volume on general pathology first appeared in 1908 and the volume on special pathology in 1909. The two were later combined in a *Textbook of Pathology: General and Special* (1925) that for many years was the standard work on pathology in Britain.

In 1907 Beattie was appointed to the chair of pathology and bacteriology at Sheffield, and during the five years that he held that appointment he was also dean of the medical faculty and honorary pathologist to the Sheffield Royal Infirmary and Sheffield Royal Hospital. In 1912 he accepted the post of professor of bacteriology in the University of Liverpool, which carried with it the duties of city bacteriologist. He held this appointment until his retirement in 1934, and in the following year Liverpool University conferred on him the title of emeritus professor.

In Sheffield Beattie continued his studies on the causal relation of streptococci to acute rheumatic disease and became interested in the pathology of the dust diseases and their relation to tuberculosis. The duties of city bacteriologist in Liverpool turned his attention to public health bacteriology, and during the later part of his career his published papers were concerned with bacteriological diagnosis of anthrax, cerebrospinal meningitis, tuberculosis due to milk, sterilization of milk, the bacteriology of water supplies, and similar topics. In recognition of his eminence in this particular field he was honoured by the National University of Ireland, which in 1933 conferred on him the honorary degree of D.Sc. in public health.

Although Beattie made considerable contributions to bacteriology in its relation to public health, it is perhaps Beattie and Dickson's *Textbook of Pathology* that will ensure his place amongst our eminent pathologists. In his years of retirement he devoted much time and care to the revisions necessary for later editions of this book, the fifth of which appeared in 1948. He also wrote *Post Mortem Methods* (1915), and he was the editor of the pathological sections of Choyce's *System of Surgery*.

A member of the British Medical Association for nearly fifty years, he was a vice-president of the Section of Pathology when the Association held its Annual Meeting at Sheffield in 1908; a vice-president of the Section of Bacteriology at Liverpool in 1912 and at London (Centenary Meeting) in 1932; and president of the Section of Pathology and Bacteriology at the Dublin Meeting in 1933. From 1932 to 1935 he represented the University of Liverpool on the General Medical Council. He was formerly examiner in pathology for the National University of Ireland, the Universities of Edinburgh, Glasgow, Aberdeen, St. Andrews, Birmingham, Bristol, London, Belfast, and Durham, and Trinity College, Dublin.

A year after his retirement from the University of Liverpool, Beattie was invited to take charge of the department of pathology in Aberdeen during the absence through illness of the late Professor Shennan. Beattie thoroughly enjoyed this return to the teaching of pathology. His lectures were popular and greatly appreciated by the students in Aberdeen. He was a very good teacher; his lectures were clear, simple, and concise, and, although with undergraduates he may have been rather dogmatic, his teaching to postgraduates was thorough, discursive, and stimulating. His tall, lean, slightly stooping figure rather belied a very warm nature, of which a most engaging chuckle gave frequent outward expression. His was a many-sided likable personality, and he enjoyed a very happy family life. Throughout his life he devoted much time to the affairs of the English Presbyterian Church.

Professor Beattie married Miss Margaret Kettle, second daughter of Mr. Thomas Kettle, of Kilmarnock. His widow survives him together with a daughter and a son, Mr. W. M. Beattie, who is on the staff of the medical school of Liverpool University.—A. W. D.

J. D. A. G. writes: By the death of Professor J. M. Beattie the profession has lost a most distinguished member. His attainment of the great age of 87 made him comparatively unknown to many of the younger generation of pathologists. Beattie was an original member of the Pathological Society, which is to celebrate its half-centenary next year. In addition to his joint authorship of the well-known textbook of pathology, his name will be remembered for his outstanding contributions on the cells of inflammatory exudations and on the electrical sterilization of milk. Though at heart he was a histologist rather than a bacteriologist, in his last letter to me written a few weeks before his death he wrote: "I look back with a great deal of pleasure on my work both in Sheffield and in Liverpool. They were happy days." Never was a man more deserving of happiness in his work.

Although to some who did not know him well his appearance suggested austerity, natural shyness, modesty, and humility were among Professor Beattie's characteristics. He was a deeply religious man. This feature never obtruded itself, but was the key to his whole outlook on life. He continually strove to live up to the high ideals which he set before himself. One of his professorial colleagues in Liverpool once said of him, "If anyone has a quarrel with Professor Beattie I am willing to wager it will not be Beattie's fault." His courtesy and kindness were quite outstanding. He took a very deep interest in his assistants, helping them in every possible way—not only as regards their work but in their enjoyment of life. He championed the rights of his technicians, and enabled several of them to acquire qualifications which would otherwise have been impossible for them. Those who were privileged to enter his home realized at once his dignity and kindness and how happy a place it was. To his widow and his two surviving children (both members of the medical profession) the sympathy of their many friends go out.

L. C. THOMSON, Ph.D., M.B.

Dr. L. C. Thomson, formerly director of the Medical Research Council's Group for Research on the Physiology of Vision, died in the London Hospital on October 10, aged 42.

Lewis Charles Thomson was born on April 30, 1913. He studied medicine at Guy's Hospital, winning the Michael Harris Anatomy Prize in 1934, and graduating M.B., B.S. in 1938. He did not turn to the study of physiology until some years later, taking the Ph.D. degree of London University in 1948. After holding the post of lecturer in physiology at Guy's Hospital, he joined the staff of the Medical Research Council, working in the Physiology of Vision Research Unit. Later he was appointed director of the Group for Research on the Physiology of Vision, and he was also a teacher of physiology at the Institute of Ophthalmology.

J. A. B. G. writes: L. C. Thomson, engaged as he was in research on visual problems, and in particular those connected with colour vision, was in a field at once active and controversial. He thus became a familiar figure in the discussions of the Physiological Society and of the Physical Society's colour group. Physiologists will remember him as he rose slowly in his place after a communication had been opened for discussion and, with the greatest good humour, criticized the case presented in the paper, emphasizing his points by a slight raising of the voice and a gesture of the hands. In spite of taking up physiology comparatively late in life, he made a considerable number of original contributions in his field and in particular to the study of the spectral sensitivity of the fovea. In recent years he attempted an analysis of retinal activity by recording the impulses in single fibres of the optic nerve while stimulating single receptors with controllable light flashes. He overcame very considerable technical difficulties in developing this method, and it is a great loss to physiology that he should have died before he was able to exploit his technique to the full. He was known to a wider audience for his lectures and reviews on colour vision; thorough and vigorous, these were of great value not only to those working on the eye but to anyone concerned with the physiology of sensory and other nervous activity. His ability to inspire others is well shown by the activity of the group he directed—that is, the Medical Research Council's Group for Research on the Physiology of Vision—and by the number of new graduates who, as a result of his influence, have chosen to work on visual problems. He did much for the Physiological Society, and many will remember his efforts in organizing transport and currency for those who attended the International Congress of Physiology in Montreal. He was an officer and finally chairman of the colour group of the Physical Society and was one of those most responsible for its activity.

Those of us who were privileged to know him personally will remember him for his great enthusiasm, whether it was in upholding the trichromatic theory of colour vision, in working for the Home Guard, or in discussing the yacht he had built a few years ago and which he was sailing when he was taken ill for the last time. There are many who are grateful for help that he was always willing to give. He will be remembered with affection.

BRIAN DONNELLY, M.R.C.S., D.M.R.

Dr. Brian Donnelly, consultant radiologist to the United Cambridge Hospitals and the East Anglian Regional Hospital Board, died in Cambridge on October 8 after a very short illness. He was 42 years of age.

Brian Donnelly was born on January 30, 1913. He was educated at Worksop College, Nottinghamshire, and at the Victoria University of Manchester and Manchester

Royal Infirmary, where he qualified M.R.C.S. in 1938. His first appointment was as house-surgeon at St. Mary's Hospitals, Manchester, and from there he proceeded to the post of assistant medical officer at the Royal Manchester Children's Hospital. After nine months in the industrial areas of Lancashire as a general practitioner he decided to take up radiology and studied at the radiological department of the Edinburgh Royal Infirmary. After he had obtained the D.M.R. at the University of Edinburgh in 1941 he joined the R.A.F., in which he served for five years. During the first two years of his service he was radiologist at Princess Mary's R.A.F. General Hospital, Halton, and at the R.A.F. General Hospitals at Ely, St. Athan, and Cosford. For the next two years he was radiological specialist to the R.A.F. General Hospital, Evesham, and to No. 10 R.A.F. General Hospital, Karachi. He planned in detail the new radiological department for the No. 10 R.A.F. General Hospital, which was the largest R.A.F. hospital in the Far East, and he also planned a number of other smaller *x*-ray departments in India. During the last year of his service in the R.A.F., holding the rank of squadron leader, he was adviser in radiology to Base Air Forces, South-east Asia, and subsequently to the R.A.F. in India and to the Air Command, South-east Asia. In the course of his duties he undertook the reorganization of the *x*-ray department of a hospital in Singapore after it had been taken over by the R.A.F. from the Japanese. In October, 1946, after demobilization, he obtained the post of assistant radiologist at Addenbrooke's Hospital, Cambridge. With the changeover to the National Health Service he became first assistant, with consultant status, in the diagnostic department of Addenbrooke's Hospital, and in December, 1951, he was made a full consultant radiologist to the United Cambridge Hospitals and also consultant radiologist to the East Anglian Regional Hospital Board, with charge of the *x*-ray department, at Huntingdon County Hospital. For a number of years before his death he was honorary secretary to the consultant staff committee, and served on several other committees of the United Cambridge Hospitals and at Huntingdon County Hospital. Among his other appointments was that of associate lecturer in radiology to the University of Cambridge, and the degree of M.A. was conferred upon him. Subsequently he was made a member of Trinity College. Besides giving lectures on his subject, he took part in the organization of the School of Radiography in Cambridge.

Brian Donnelly's main interests in radiology were paediatrics and the oesophagus, and he published several papers on these subjects. His experimental work on the functions of the cardia was well devised, and some of his observations were published in 1952, when the British Institute of Radiology awarded him the Barclay Prize for an essay on "Gastro-oesophageal Regurgitation and Oesophageal Hiatus Hernia, with Special Reference to the Differential Diagnosis of Angina Pectoris." He was, in fact, the first person to win this prize after its foundation. He also contributed a paper on achalasia of the oesophagus at the seventh International Congress of Radiology at Copenhagen. Another of his interests was cardiology, and he undertook all the radiology for the cardiac clinic at Addenbrooke's Hospital.

He was a charming colleague to work with and had a most imperturbable temperament—nothing ever appeared to upset him. Yet his was the reverse of a cold personality: he was generous and warm-hearted, and had a keen sense of humour. He did his work so quietly and efficiently that it was his absence from any cause that brought home to his colleagues in the department the very great contribution which he made to it. Outside the hospital he also had many friends, but he was essentially a family man and his real sources of happiness were being with his family and the cultivation of his garden. His passing will leave a gap in Cambridge which it will not be easy to fill. Not only will he be sadly missed in the *x*-ray department, of which he seemed such an integral part, but he will be mourned by all his former colleagues.

In 1935 Dr. Donnelly married Betty Brotherton, daughter of the late Richard Brotherton, of Richard Brotherton Ltd., cotton shippers, of Manchester, and they had one son. His widow and son survive him.—F. R. B.

W. S. H. writes: Those who knew Brian Donnelly will treasure the memory of his personal charm and quiet, unassuming manner. As a student in Manchester and Edinburgh, a squadron leader in the Royal Air Force, and a consultant radiologist in Cambridge he pursued his studies and carried out his work with the same steadfastness of purpose. The keenness and enthusiasm which he showed in his early life on the rugby field were to be seen later in his garden and in the *x*-ray department. The knowledge of the impending tragedy did little to dim his cheerful outlook, and those in close contact with him realized his fortitude and courage. He will be sadly missed by all who knew him, but as a devoted husband and proud father he is mourned most by his widow and son, to whom all extend their deepest sympathy.

MARGARET N. JACKSON, B.M., D.P.M.

Dr. Margaret Jackson, who died in the London Hospital on October 14 after a few days' illness, had been an assistant editor of the *Lancet* for fifteen years. Outside this regular work, she was known as an able writer, especially on the problems of nursing and on the investigation and better management of mental disorder. She had collaborated with the late Dr. Harry Roberts in his *Everyman in Health and Sickness*, and she wrote the chapters on insanity in his *The Troubled Mind*.

Born in 1901, Margaret Nelson Jackson was the daughter of the late Nelson Jackson, well known as a Lancashire comedian and entertainer and well liked by fellow members of the Savage Club. From St. Paul's School for Girls she went to Somerville College, Oxford, and Charing Cross Hospital, where she graduated B.M., B.Ch. in 1926 and was a house-physician. She then went out to Egypt as medical superintendent of Lady Cromer's dispensary in Cairo, where she looked after sick infants. In 1931 she was secretary of the *Lancet* Commission on Nursing, and acquired her lasting interest in the training and tasks of the nurse. This was broadened by two years' work in a private mental hospital and six at the Fountain Hospital, where she had charge of mental defectives. In 1935 she took the D.P.M.

After she joined the *Lancet* her determination to improve conditions for the mentally afflicted led her to write a great deal on this subject; but she put almost as much persistent effort into the other major problems of social medicine—the care of the old and the very young, the prevention of delinquency, the rehabilitation of the ill, and the management of tuberculosis. Her associates valued her both for the vigour and freshness of her writing and for her inexhaustible reserves of gaiety and friendship. Her talent for easy, lively, accurate, and fair-minded exposition could be used with equal effect

for different kinds of audience, and various national bodies had latterly enlisted her aid in persuading the public. In the last ten years she had written in *Home and Country* (the magazine of the National Federation of Women's Institutes) on such subjects as the upbringing of children and the changing attitude to mental illness, while one of her last tasks was to prepare a pamphlet for the Ministry of Health.

A colleague writes: Margaret Jackson's attitude to neurosis, to psychosis, and to mental defect was different from the ordinary. It was one of acceptance of people as they are, not of objection to their deviation from some ideal. Between her and her patients there was no door to be formally unlocked: she felt that, like everybody else, they had their limitations, but she liked them for themselves as much as though they were normal. When her own interest or sympathy was engaged—and she was a woman of wide interests and very ready sympathy—she was singularly generous. To help in a reform in which she believed, her energy, her money, and her wit were given as freely as they were given in any emergency in the life of a friend.

E. M. C. writes: Dr. Margaret Jackson had a delightfully dry sense of humour, and at the same time she was one of those quiet people who leave an indelible impression of integrity. At the beginning of the war, when she was working at the Fountain Hospital, caring for grossly mentally deficient children, she told me of her extreme and urgent preoccupation with air-raid precautions, aimed to save these not very promising young lives. Close identification with her work meant that when her advice was sought on any point in medical journalism she gave her whole attention to the task in hand.

ALEXANDER LIVINGSTON, M.B., M.D.S., L.D.S.

Dr. Alexander Livingston, formerly sub-dean of King's College Hospital Dental School and later principal of the Queensland College of Dentistry, died in Oxford on September 28 at the age of 61.

Alexander Livingston was born in Glasgow and educated at Wellington High School, near Liverpool, and at Liverpool University. Although lame from childhood, he enlisted in August, 1914, for special service with the Royal Engineers in a unit concerned with wireless signalling. He returned to Liverpool in 1916 to complete his dental and medical education, gaining distinctions in dental materia medica, metallurgy, and mechanics. He took the B.D.S. degree in 1918 with further distinctions, and was appointed dental surgeon to the Liverpool Royal Children's Infirmary. Towards the end of his student career he was president of the Liverpool Guild of Undergraduates. He proceeded to the M.D.S. degree in 1919 and took the degrees of M.B., Ch.B. in 1921. After qualification he held the posts of honorary pathologist to the Liverpool Eye and Ear Infirmary and demonstrator of dental anatomy, histology, and pathology at Liverpool University.

Livingston was appointed a member of the Committee on Diet and its Relation to the Teeth (a subject which was his main interest throughout his life) by the British Dental Association in 1922, and later became chairman of the Research Committee of the Metropolitan Branch of the B.D.A. In 1923 he was appointed sub-dean of the new dental school of King's College Hospital and director of dental studies there. He helped to initiate, and himself organized, the new school with great energy and originality of mind. It had become by 1931 one of the most advanced of its kind. While at King's, Livingston was lecturer in dental surgery and pathology in the University of London, and in 1927 he was appointed consulting dental surgeon to the London County Council. He published the results of research work on the incidence and cause of dental caries, and in 1929 wrote a handbook of dental histology. Always a keen supporter of the King's rugby side, he was often to be seen on the touch-line at Dog Kennel Hill.

In 1931 he took up new appointments as principal of the new Brisbane Dental Hospital, and principal of the Queensland College of Dentistry in the University of Queensland. The combination of the two posts gave scope to his outstanding gifts as lecturer, teacher, and organizer. The plans for a new dental hospital at Brisbane bore the imprint of his ideas, and the training of students there soon reached a high standard. He was examiner to the Universities of Queensland and of Melbourne, and a member of the Advisory Medical Committee of the Queensland Cancer Trust, for cancer of the mouth was one of his great interests.

He came back to England, and to private practice, in 1934. Recurrent ill-health interfered with his work, and more than once, after an absence of six months or more, he had to start again from the beginning—or rather from a nucleus of patients waiting for his return, sooner than going elsewhere for treatment. In Southampton, where he first settled, his interest in research and in dental administration persisted. In 1945 he published observations on diet in relation to gingivitis. He was chairman of the Southampton Section, Wessex Branch, of the British Dental Association from 1937 to 1947, and of the Joint Committee for Industrial Dentistry from 1943 to 1947.

His last six years were spent in Oxford. He was a member of the local dental committee, and his views on controversial subjects were always well balanced and carefully thought out. During the last few months of his life he endured great pain, but was seeing and treating his patients within six days of his death.

In his later life Dr. Livingston maintained a keen interest in local affairs, in his old students, and in much else besides: he had a wide scientific and humanitarian knowledge; he was a competent model engineer, and a lover of birds, of books, of music, and of gardening; and he was fond of painting in oils tiny glimpses of his native land. He will be missed by all those who had the privilege of being included in the circle of his friends. He married in 1926 Miss Margaret Aubrey Edwards, who survives him together with a son and a daughter.

The many friends of Dr. Nathan Dembovitz and his colleagues both at St. George's and the Wimbledon Hospital were shocked to hear of his sudden death on September 29 at the early age of 39, while he was at work in his consulting-room. Nathan Dembovitz was born on October 24, 1915, and received his medical education at St. George's Hospital. He showed a special interest in psychiatry even as a medical student, and, after qualifying in 1939, worked for a time at Claybury Mental Hospital, taking his D.P.M. in 1940. In the R.A.M.C. he served as a specialist in psychological medicine with the rank of major. After the war he became a registrar at St. George's, and was subsequently appointed senior hospital medical officer in the psychiatric department there. He also held an appointment at the Wimbledon Hospital. Soon after his return to St. George's he took charge of the electric-convulsive-therapy clinic, which he had conducted ever since with great efficiency and skill.

Dr. Desmond Curran writes: Nathan Dembovitz was an excellent clinician and a man with a most engaging and

cheerful personality. He had wide interests outside medicine, and was highly cultivated and civilized, with a special knowledge of painting and furniture. He was a delightful companion and an excellent talker, and not only his patients but many of his colleagues would remark how the world seemed a better and more worth-while place after meeting him. He had a sunny and equable disposition, which, coupled with the care and kindness he always showed, made him specially suitable for the branch of medicine he had chosen. He will be greatly missed, and I am sure that the many patients who remember him with gratitude will wish to join us in sending our deepest sympathy to his wife and family.

Medico-Legal

NEW TRIAL ORDERED IN SILICOSIS CASE

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In 1929 or 1930 Walter Richards became a moulder in the employment of Highways Ironfounders (West Bromwich) Ltd. He worked in Room C, a large room with a floor of sand except for a concrete alley-way, filling moulds with molten metal, and when the moulds were somewhat cooled opening them and taking out the cooling forms. In the course of this last process, known as "knocking out," adherent grains of sand are manually knocked off the castings, and it is very dusty, emitting clouds of sand. There was no synchronization organized among the men in Room C, so that an operative even when not subjected to thick dust clouds emitted from his own moulds was more, or less continuously immersed in the clouds emitted by his fellow workers' operations.

Until 1950 it was not appreciated that the process, however uncomfortable, was dangerous to health. But it was then established that it caused fracture of the grains of sand, which emitted minute fragments of silicon dioxide, and these if inhaled in sufficient quantities are apt to produce silicosis.

By 1946 Richards was seriously affected with silicosis. By 1948 he was dangerously and incurably ill. By 1954 he was largely incapacitated from work, and had an expectation of life of about 15 years. He was then in his forties. In that year he brought an action against his employers, and his case, based on s. 47 of the Factories Act, 1937, was that they ought to have provided him with a mask or respirator.

The evidence at the hearing was that it would have taken about 15 years of exposure to the lethal fragments of sand for a man in Richards's job to become dangerously and incurably ill. In 1950 there were as many as 20 types of respirator or mask available to protect workers against the inhalation of large quantities of dust, but in the light of later knowledge only one of these, the Mark IV, would have been effective against the minute particles of silicon dioxide.

Mr. Justice Devlin, who tried the action, decided that Mark IV masks ought to have been provided, and awarded £9,645 damages, of which £200 was for loss of expectation of life, £7,000 for loss of earning capacity, and £1,000 for Richards's loss of the prospect of making provision for his wife and other dependants.

On appeal[1] the Court of Appeal held that the £1,000 for loss of ability to make provision for dependants was not recoverable as damages as a matter of law. They directed a new trial on the question whether failure to provide Mark IV masks was a breach of the employers' obligation under s. 47, and, if so, to what extent Richards's condition was caused by their absence, since he had been in his job for 10 years before the masks became available.

[1] *Richards* v. *Highways Ironfounders (West Bromwich) Ltd.*, [1955] 1 W.L.R. 1049.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 1** (No. 39) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	10	1	4	0		11	0	8	0	
Dysentery	427	61	238	16	4	369	43	172	4	5
Encephalitis, acute	4	0		0		3	0	0	1	
Enteric fever:										
Typhoid	5	0	1		3	6	0	0	1	1
Paratyphoid	45	4	3(B)	19		7	0	2(B)	0	1(B)
Food-poisoning	325	32		7		258	25		1	
Infective enteritis or diarrhoea under 2 years					75				18	16
Measles*	1,227	32	25	15	37	1,833	125	246	24	144
Meningococcal infection	22	2	11	1		23	0	12	2	1
Ophthalmia neonatorum	39	3	5	0		27	0	4	0	
Pneumonia†	228	18	115	3	5	324	17	111	2	1
Poliomyelitis, acute:										
Paralytic	207	31	48	3		46	1	15	1	3
Non-paralytic	180	29				24	3			
Puerperal fever§	241	34	11	3		247	50	10	2	
Scarlet fever	550	30	87	23	22	546	35	119	26	17
Tuberculosis:										
Respiratory	710	85	102	13		680	112	107	10	
Non-respiratory	101	9	12	4		95	4	29	2	
Whooping-cough	993	55	50	55	67	1,464	66	114	8	41

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	0	2	1	2	4	0		1	1
Influenza	5	1	0	0	0	5	0	0	0	0
Measles		4	0	0	0		0	0	0	0
Meningococcal infection		0	2				1	1		
Pneumonia	145	9	15	4	5	152	23	15	6	2
Poliomyelitis, acute	8	1			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	48	5	8	0	4	70	9	10	1	8
Non-respiratory		0	0	0	1		3	11	0	1
Whooping-cough	1	0		0	0	4	0	0	0	0
Deaths 0–1 year	201	27	11	13	15	183	23	21	7	17
Deaths (excluding stillbirths)	4,421	617	62	91	152	4,657	630	568	114	152
LIVE BIRTHS	7,493	1131	867	240	447	7,608	1103	853	218	478
STILLBIRTHS	192	24	20			178	23	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Poliomyelitis

For the first time since the present outbreak began the number of paralytic cases in England and Wales in the week ending October 8 fell substantially below the previous week's total. The figures for the week (with those for the previous week in parentheses) were: paralytic 186 (207); non-paralytic 164 (180); total 350 (387). Deaths in the great towns numbered 7. Notifications from the beginning of the year up to October 8 numbered 4,988. Only in 1947 and 1950 were they more numerous—namely, 7,095 and 6,718 respectively.

The incidence of the disease increased in the north-midland and south-western regions of England and in Wales; it decreased elsewhere. The following districts have had particularly high rates to date (figures are for cases notified up to October 8, with rates per 100,000 of the population in parentheses): Mexborough U.D. 21 (110.4), Barnsley C.B. 77 (102.2), Willesden M.B. 160 (90.2), Hoyland Nether U.D. 13 (81.9), Wombwell U.D. 13 (69.2), Cheshunt U.D. 16 (63.1), Clacton U.D. 14 (58.1), Aylesbury M.B. 12 (56.6), Stepney M.B. 53 (56.2), Dover M.B. 19 (55.8).

In Scotland 40 cases were notified, 8 fewer than in the previous week. 20 of them were reported from Glasgow, 10 fewer than in the previous week.

Poliomyelitis Vaccine in U.S.A.

According to the United States Secretary of Health (Mr. Marion B. Folsom), preliminary data show that the incidence of poliomyelitis among about seven million vaccinated children, most of whom have received only one injection, is running roughly 25 to 50% below the rate among non-vaccinated children in the same age groups. Since revised production and testing standards were adopted last May, he added, there has been no association of poliomyelitis with any vaccine released for use.

Week Ending October 8

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 666, whooping-cough 802, diphtheria 6, measles 1,397, acute pneumonia 237, acute poliomyelitis 350, dysentery 475, paratyphoid fever 41, and typhoid fever 5.

Infectious Diseases

In England and Wales during the week ending October 1 the largest fluctuations in the number of notifications of infectious diseases were a decrease of 120 for whooping-cough, from 1,113 to 993, an increase of 145 for measles, from 1,082 to 1,227, and 124 for scarlet fever, from 426 to 550.

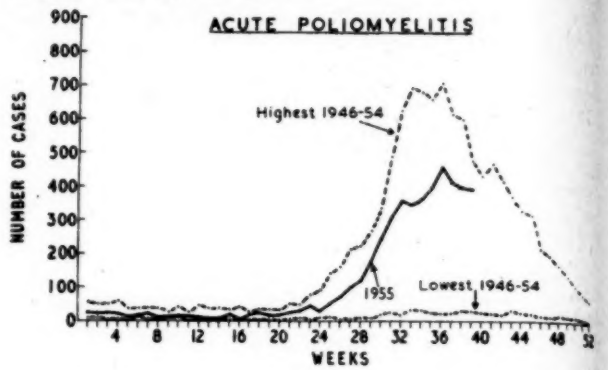
The largest rise in the incidence of measles was 35 in Devonshire, from 43 to 78. The largest fluctuation in the returns of scarlet fever was a rise of 25 in Yorkshire West Riding from 62 to 87. A small fall in the incidence of whooping-cough was recorded in most regions; the largest fall was 21 in Essex, from 47 to 26. 10 cases of diphtheria were notified, being 4 more than in the preceding week. 3 cases of diphtheria were notified in Plymouth C.B. and 2 in Huyton-with-Roby U.D., Lancashire.

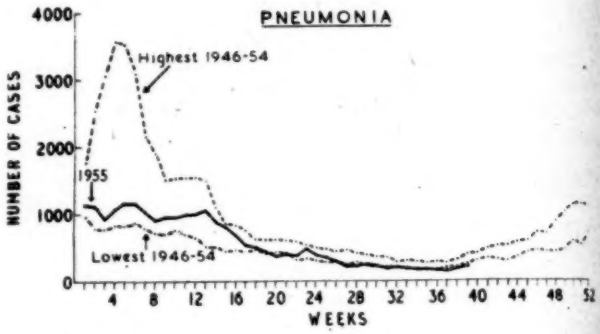
The notifications of paratyphoid fever decreased by 24, from 69 to 45. A further 11 cases were notified in the outbreaks in Nottinghamshire, bringing the total notifications in this county to 163 cases in the past four weeks.

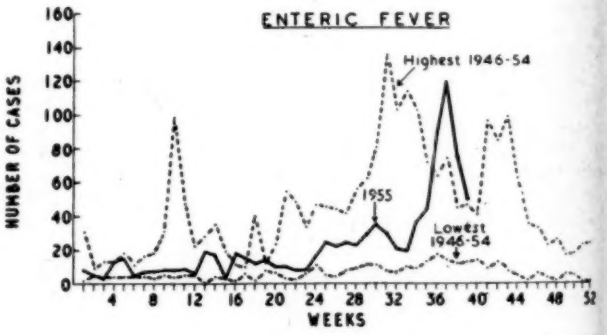
427 cases of dysentery were notified, and these were 23 fewer than in the preceding week. The largest centres of infection were Lancashire 115 (Liverpool C.B. 38, Haslingden M.B. 18, Stretford M.B. 13, Blackpool C.B. 10), London 61 (Chelsea 19, Southwark 17), Yorkshire West Riding 61 (Leeds C.B. 30), Warwickshire 25 (Birmingham C.B. 14), Durham 24, and Middlesex 18.

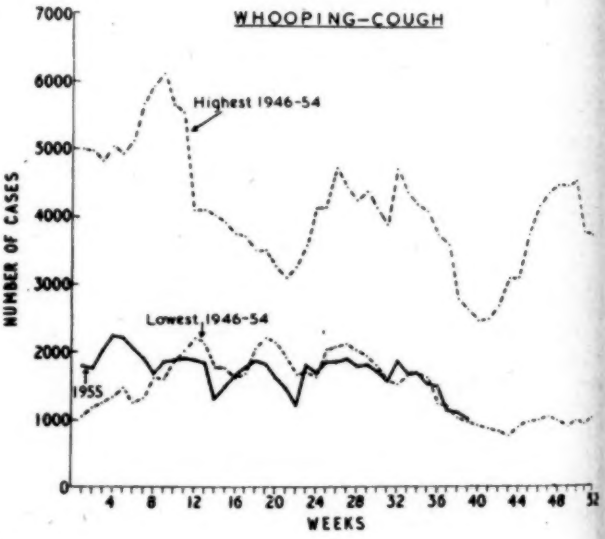
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus - - - - - -, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Medical News

The Nuffield Provincial Hospitals Trust is to invest £200,000 over the next five years in the development of the health services of Harlow. Three group practice and clinic centres have been completed, and were opened by Lord Nuffield on October 17. These will be used by general medical and dental practitioners and by the Essex County Council Health Authority. Three similar buildings will be built over the next few years to meet the health needs of an ultimate population of 80,000. The present building will house clinics for infant welfare and ante- and post-natal care. Orthopaedics, ophthalmology, speech-therapy, and child-guidance will be served by clinics in a special building. From November a non-profit-making company of industrialists will operate an industrial health service for the 5,766 people at present working in Harlow. The Nuffield Trust, which is providing accommodation, has made an outright grant to the service to meet its estimated deficiency on running costs until it can become self-supporting in three years' time. The Trust aims to evolve a pattern of comprehensive medical care in Harlow which may prove a future guide to other communities.

Offences of Drunkenness.—A slight decline in the number of proved offences of drunkenness in 1954 was again recorded for England and Wales. The total number was 53,377, giving a rate of 15.52 per 10,000 population aged 15 and over. The peak year since the war was 1952, with a rate of 15.78. In 1938 the rate was 16.84, though comparisons over more than a few years are apt to be difficult to interpret because police activity may vary and the views of magistrates alter. In the local statistics, London heads the list with 246 offences per 10,000 population aged over 15; this figure is artificially inflated by the relatively small resident population from which the rate is derived. Next come Newcastle-upon-Tyne 64.8, Birmingham 52.4, Liverpool 52.3, and Middlesbrough 49.2. At the other end are Norwich 3.4, Cambridge 3.0, and Bristol 2.1. The placing of these cities has been much the same in previous years. The average rate for the counties in England was 5.6 and for the cities 15.9; in Wales and Monmouthshire the corresponding rates were 6.7 and 9.8 respectively.

Photographic Exhibition.—Some recent developments of photography in the service of medicine are included in an exhibition staged at the Royal College of Surgeons until October 29. Some stereoscopic radiographs, photographs, and diagrams show what an advantage "3 D" can be in recording abnormalities of such subjects as the heart and hand. The well-known effect of infra-red rays in showing up the cutaneous veins is displayed, and in addition the less often seen results of illumination with ultra-violet rays, which reveal the skin and its appendages with startling clarity. Another exhibit shows what can be achieved with xero-radiography, which entails the development of the image, photographic or radiographic, by means of powder on a magnetized screen. Also on view are about 100 black-and-white prints and 50 colour transparencies. Nearly all are of the highest quality and show in exemplary fashion how useful a medium photography can be for keeping records. However, rather too many of them are of common subjects which can be seen in actuality any day in the ward or post-mortem room. The exhibition is open from 10 a.m. to 6 p.m. daily (to 8 p.m. on Wednesday).

Juvenile Epilepsy.—On October 6–12 fifteen specialists from nine countries met in London under the auspices of the World Health Organization to discuss juvenile epilepsy. Among their recommendations was the formation of diagnostic and treatment centres with modern methods of treatment. Ever fewer children would need even semi-permanent institutional care, and the emphasis would be on keeping handicapped children so far as possible in the normal community. A full report will be available in due course from W.H.O. Those participating were: Professor Fraser Brockington (England), Dr. Romanes Davidson (England), Professor H. Gastaut (France), Professor J. R. Hargreaves (England), Dr. Peter Henderson (England), Dr. H. Landolt (Switzerland), Dr. B. Ch. Ledeboer (Netherlands), Dr. William Lennox (U.S.A.), Dr. Karl-Axel Melin (Sweden), Dr. Julius Metrakos (Canada), Dr. F. Sal y Rosas (Peru), Dr. Hans Strotzka (Austria).

Association of Clinical Biochemists.—At the Annual General Meeting, held at the Royal College of Surgeons on October 1, the following officers were elected: President, Professor N. F. Maclagan (Westminster Medical School); chairman, Dr. C. P. Stewart (Royal Infirmary, Edinburgh); treasurer, Dr. I. MacIntyre (Postgraduate Medical School of London); secretary, Dr. A. L. Tarnoky (Royal Berkshire Hospital, Reading).

Railway Medical Services.—The 6th Congress of the International Union of Railway Medical Services was held at Dubrovnik, Yugoslavia, on September 19–24. The subject was "Lumbago and Sciatica among Railway Personnel." British contributors included Dr. J. Sharp Grant and Dr. G. E. Graves Peirce, both of British Railways. Dr. C. T. Newnham, also of British Railways, illustrated rehabilitation in the Western Region by means of a film.

Leukaemia Research.—Dr. R. H. Mole, of the Atomic Energy Research Establishment, Harwell, has received the first grant of the American Leukemia Society to be awarded outside the United States. He will study the effects of irradiation on leukaemia.

Mr. F. W. Law has been elected Master of the Worshipful Company of Spectacle Makers.

COMING EVENTS

Handicapped Child.—A conference on "The Handicapped Child," to which general practitioners, doctors in the public health service, and paediatricians are invited, will be held at the Highgate Wing of the Whittington Hospital, Dartmouth Park Hill, London, N.19, October 29, 2–5.30 p.m. Drs. R. MacKeith and A. Mower White will be opening speakers, and Dr. J. D. Kershaw will be in the chair.

Christian Medical Education in India.—A meeting will be held on November 1 at 5.30 p.m. at Manson House, 26, Portland Place, London, W.1, in connexion with the work at Vellore and Ludhiana Medical Colleges. There will be speakers from both colleges, and Dr. C. C. Chesterman will be in the chair. Invitation cards from the secretary, Medical Missionary Association, 31, Bedford Place, London, W.C.1.

Contraceptive Technique.—Lecture and demonstration by Dr. Marie Stopes at the Mothers' Clinic, 108, Whitfield Street, London, W.1, on November 3 at 5.15 p.m. No fee is charged, but tickets must be obtained in advance.

Royal Free Hospital Medical Society.—The inaugural meeting will be held at the Medical School on October 27 at 6.30 p.m. The chair will be taken by Sir Daniel Davies, President of the Society, and the inaugural address will be given by Sir Lionel Whitby, Regius Professor of Physic in the University of Cambridge, who will speak on "Medicine and Medical Societies."

Ischaemia.—Professor J. H. Dible will deliver the Kettle Memorial Lecture on "Ischaemia in the Peripheral Circulation" at the Institute of Pathology, Royal Infirmary, Cardiff, on December 2 at 5 p.m.

Fourth International Congress of Internal Medicine.—September 19–23, 1956, in Madrid. The two main subjects for discussion are: (1) The role of the adrenals in the pathogenesis and evolution of internal diseases. (2) Bronchial asthma and emphysema. Details from Drs. J. C. de Oya and J. Gimena, Hortaleza 90, Madrid.

NEW ISSUES

British Journal of Venereal Diseases.—The new issue (Vol. 31, No. 3) is now available. The contents include:

EDITORIAL.
STUDIES ON THE REPRODUCIBILITY AND SPECIFICITY OF THE TREPONEMAL IMMOBILIZATION TEST. P. J. L. Sequeira and A. E. Wilkinson.
STUDIES ON THE TREPONEMAL IMMOBILIZATION TEST. III. USE OF THE TPI AS A VERIFICATION TEST IN SUSPECTED LATENT SYPHILIS. A. E. Wilkinson and P. J. L. Sequeira.
THE MALE GONORRHOEA "CARRIER." REPORT OF SEVEN CASES. J. B. Bittiner and G. O. Horne.
BENZATHINE PENICILLIN IN THE MANAGEMENT OF THE TREPONEMATOSES. T. Guthe.
PERIPHERAL NEURITIS ASSOCIATED WITH A PULMONARY LESION IN A PATIENT WITH SYPHILIS. G. H. Knight and W. Fowler.
LYMPHOGRANULOMA VENEREUM (LYMPHOGRANULOMA INGUINALE). T. Lyall.
USE OF AN INDIVIDUAL UNSATURATED LECITHIN FROM YEAST IN ANTIGENS FOR THE SERO-DIAGNOSIS OF SYPHILIS. David B. Tonks and Rovelle H. Allen, with the technical assistance of Evelyn Fowler.
ASYMPTOMATIC NEUROSYPHILIS IN HONG KONG. G. M. Thomson.
ERYTHROMYCIN AND TETRACYCLINE HYDROCHLORIDE IN THE TREATMENT OF NON-GONOCOCCAL URETHRITIS. R. R. Willcox.
INTRAMUSCULAR TETRACYCLINE (ACHROMYCIN) IN THE TREATMENT OF ACUTE GONORRHOEA IN THE MALE. Milton Marmell and Aaron Prigot.
VENEREAL DISEASE PHOBIA IN THE SEVENTEENTH CENTURY. A. Fessler.
ABSTRACTS.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Thorax.—The new issue (Vol. 10, No. 3) is now available. The contents include:

SURVIVAL AFTER LUNG RESECTION FOR BRONCHIAL CARCINOMA. J. R. Bignall and A. J. Moon.
"MODIFIED" THORACOPLASTY. T. Holmes Sellors, J. W. Jackson, and J. G. Callanan.
SELECTION OF TISSUE FOR MICROSCOPIC STUDY FROM LUNGS INJECTED WITH RADIO-OPAQUE MATERIAL. Lynne M. Reid.
CORRELATION OF CERTAIN BRONCHOGRAPHIC ABNORMALITIES SEEN IN CHRONIC BRONCHITIS WITH THE PATHOLOGICAL CHANGES. Lynne M. Reid.
DEVELOPMENTAL DEFECTS IN THE LUNGS. P. Jones.
THE PARASTERNAL DEFECT. E. F. Chin and E. R. Duchesne.
A CLINICO-PATHOLOGICAL STUDY OF ATELECTASIS IN PULMONARY TUBERCULOSIS. Leslie J. Temple.
RESECTION OF TUBERCULOUS STRICTURES OF THE MAIN BRONCHI IN THREE CASES. J. W. Jackson, P. H. Jones, and T. Holmes Sellors.
SEMI-CONTINUOUS LEFT ATRIAL PRESSURE MEASUREMENTS DURING MITRAL VALVOTOMY. Helge Baden.
VENTILATORY FUNCTION STUDIES IN EXTRAPERIOSTEAL PLOMBAGE. H. Milwidsky and H. Romanoff.
THE EFFECT OF BREATHING EXERCISES IN PULMONARY EMPHYSEMA. J. D. Sinclair.
AN ASSESSMENT OF THE VALUE OF BREATHING EXERCISES IN CHRONIC BRONCHITIS AND ASTHMA. R. S. McNeill and J. M. McKenzie.
BENIGN HISTOPLASMOSIS. Richard Leigh and Harold E. Thomas.
PNEUMOTACHOGRAPHIC MEASUREMENT OF BREATHING CAPACITY. R. J. Shephard.

Published quarterly; annual subscription £2 2s., single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 24

MANCHESTER MEDICAL SOCIETY.—(1) At Dental Hospital, 5 p.m., Section of Odontology. Dr. R. M. Forrester and Mr. J. Miller: Kernicterus and Related Dental Changes. (2) At Manchester University, 9 p.m., Section of General Practice. Dr. R. A. J. Asher: Things Are Not What They Seem.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. Pepys: Current Views on Bronchial Asthma.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor B. Mukopadhya: Role of Excisional Surgery in the Treatment of Bone and Joint Tuberculosis.

Tuesday, October 25

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. O. L. S. Scott: Systematized Naevi.
●INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. J. St. C. Elkington: Headache.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—3 p.m., Mr. F. C. Dwyer: Backache.
MANCHESTER MEDICAL SOCIETY.—At Manchester University, 4.30 p.m., University Lecture on the History of Medicine by Professor Charles Sisson: Medical Practice in Shakespeare's England: from Original Records, with a Case-history of Dr. William Harvey.
●OXFORD UNIVERSITY MEDICAL SOCIETY.—At Radcliffe Infirmary, 8.15 p.m., Dr. D. W. Woolley, Ph.D.: The New Pharmacology.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. H. G. Hanley: Urological Problems During Pregnancy.
UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, 1.15 p.m., Dr. Helen Spurway, Ph.D.: Virgin Births.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Clinical Neurology (Part II).
WEST LONDON HOSPITAL MEDICAL SCHOOL.—At Royal College of Surgeons of England, 5.30 p.m., Eighth Alex Simpson Smith Memorial Lecture by Dr. T. Russell Fraser: Tests of Thyroid Function.

Wednesday, October 26

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., joint meeting with Midland Branch of the British Psychological Society. Professor R. W. Russell: Some Effects of Certain "Biochemical Lesions" on Behaviour.
BRITISH PSYCHOLOGICAL SOCIETY: MEDICAL SECTION.—At Royal Society of Medicine, 8.30 p.m. Symposium: Jung's Contribution to Analytical Thought and Practice.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Diagnosis of Ringworm Infection.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. H. Young: Pathogenesis of Tuberculosis (III).
INSTITUTE OF UROLOGY.—At Royal College of Surgeons of England, 5 p.m., Dr. J. J. Stevenson: Cine-Radiography of the Urinary Tract; Studies of the Movements of the Urinary Tract in Health and Disease as shown by the Image Intensifier.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor N. H. Martin: Recent Advances in the Study of the Plasma Proteins.
RENAL ASSOCIATION.—At 41, Portland Place, W., 4.30 p.m., Mr. L. N. Pyrah and Dr. C. K. Anderson: Renal Calcification and Renal Stone Formation; Dr. A. D. Care: Use of Polypotassium-metaphosphate in the Prevention of Bladder Calculi in the Rat; Mr. B. T. Murphy: Crystallographic Methods Applied to the Study of Renal Stones.
●ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Dr. R. L. Richards: Peripheral Vascular Disease: The Arteries.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. J. A. Dudgeon: Recent Advances in the Control of Poliomyelitis (illustrated).
ST. MARYLEBONE HOSPITAL FOR PSYCHIATRY AND CHILD GUIDANCE.—5.30 p.m., Dr. J. Flind: Psychosomatic Syndromes.
ST. MARY'S HOSPITAL.—At Wright-Fleming Lecture Theatre, 5 p.m., Professor J. R. Squire: The Nephrotic Patient.
SOCIETY OF CHEMICAL INDUSTRY: FOOD GROUP.—At Chemical Society, Burlington House, W., 6.30 p.m., meeting of Nutrition Panel. Subject: Vitamins A and D. Speakers, Dr. T. Moore, D.Sc.: Nutritional Requirements; Dr. V. H. Booth, Ph.D.: Dietary Supplies; Mr. P. N. Williams, M.Sc., F.R.I.C.: Food Fortification.

Thursday, October 27

BRITISH ASTHMA ASSOCIATION.—At Wellcome Research Institution Hall, Euston Road, N.W., 7 p.m., Dr. F. J. Prime: Some Aspects of Inhalation Therapy.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At Beveridge Hall, Senate House, 5.30 p.m., Sir Wilfrid le Gros Clark, F.R.S.: Hypothesis and Speculation in Scientific Research.
COLLEGE OF GENERAL PRACTITIONERS.—At Worcester Royal Infirmary, 3.30 p.m., Dr. D. G. French: The Anaemias in General Practice.
GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Queen Margaret Union, 7.30 p.m., Professor E. J. Wayne: Proprietary Remedies.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., symposium: Uses and Abuses of Blood: Openers, Dr. D. Lehane, Dr. M. McCarthy, and Dr. C. A. St. Hill.
●NUFFIELD ORTHOPAEDIC CENTRE, Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Professor C. D. O'Malley: Contributions toward the Discovery of the Circulation of the Blood in the Sixteenth Century.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. J. Swinney: Hydronephrosis.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Thomas Vicary Lecture by Professor K. F. Russell: John Browne—1642-1702.
ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Aspects of Refraction—III. Investigation of the Refractive Power of the Eyes.
ROYAL NORTHERN HOSPITAL.—2.30 p.m., Mr. Alan Small: Problems of the General Practitioner and the Surgical Out-patient Department (with discussion).
ST. ANDREWS UNIVERSITY.—At Physiology Department, Queen's College, Dundee, 5 p.m., Mr. D. J. Browne: Classification and Treatment of Congenital Deformities.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. M. A. Partridge: postgraduate demonstration in psychiatry.

Friday, October 28

HONYMAN GILLESPIE LECTURES.—At University New Buildings, Teviot Place, Edinburgh, 5 p.m., Sir William P. MacArthur: History of Malaria: Past and Present.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Sir Clement Price Thomas.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—At 11, Chandos Street, W., 7.30 p.m., Dr. F. J. G. Jefferiss and Dr. J. D. W. Pearce: Venereal Disease and the Homosexual.
●SOCIETY FOR CULTURAL RELATIONS WITH THE U.S.S.R.—8 p.m., Soviet Preventive Medicine. Report by British doctors who visited U.S.S.R. in 1955.

Saturday, October 29

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—11.15 a.m., Professor A. S. Duncan: Vulvitis and Vaginal Discharge.

APPOINTMENTS

DODDS, RICHARD JOHN, M.B., B.S., D.P.H., Medical Officer of Health and Principal School Medical Officer, County Borough of Smethwick.
DONALDSON, R. J., M.B., Ch.B., D.P.H., Medical Officer of Health and Principal School Medical Officer, County Borough of Rotherham.
GROARKE, F. L., M.B., D.P.H., D.C.H., Medical Officer of Health, Area Medical Officer, and Divisional School Medical Officer, Borough of Barking, Essex.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Diggory.—On October 11, 1955, at the Old Court Clinic, Hanger Lane, Ealing, London, W., to Patricia and Dr. Peter Diggory, a daughter.

MARRIAGES

Moncrieff—Wedmore.—On October 15, 1955, quietly at Beckenham, Alan Moncrieff, C.B.E., M.D., F.R.C.P., J.P., to Mary Wedmore.

DEATHS

Debenham.—On September 17, 1955, in London, Robert Barsham Debenham, M.R.C.S., L.R.C.P.
Flory.—On September 19, 1955, Cyril Hobson Flory, M.R.C.S., L.R.C.P., of 92, Pine Vale Crescent, Bournemouth, Hants, late of Shropshire and Assam, aged 84.
Leighton.—On September 16, 1955, at St. Ives, Dorridge, Warwicks, Simon Reuben Leighton, M.D.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Menorrhagia due to Thrombocytopenia

Q.—*What treatment is advised in essential thrombocytopenia causing severe menorrhagia in a young woman aged 26?*

A.—It is of primary importance to ensure that the apparent essential thrombocytopenia is not secondary to a drug. The patient should be directly questioned with reference to individual drugs by name—for example, "aspirin," "headache powders," "quinine," etc. The general question, "Have you taken any medicine or drugs recently?" seldom obtains the whole truth.

Secondly, it must be established that there is no other cause for menorrhagia apart from the thrombocytopenia. Any haemorrhagic state may be brought to light or aggravated by local abnormality.

Essential thrombocytopenia is subdivided into acute and chronic varieties. Two avenues of active therapy are available: (1) cortisone or A.C.T.H., and (2) splenectomy.

The action of cortisone or A.C.T.H. is not fully understood, but it can promote clinical improvement in cases of thrombocytopenia purpura with or without an increase in the circulating platelets. They may induce permanent remission, but more often relapse will occur on withdrawal. Doses of either drug, larger than those commonly used, are sometimes required to elicit a response. Relapse on withdrawal does not prevent further remissions during a subsequent course of either drug.

Acute essential thrombocytopenia of sudden onset in children or young adults of either sex warrants conservative therapy with perhaps the use of cortisone or A.C.T.H. to relieve symptoms that are distressing or a dangerous bleeding tendency. Such cases usually undergo spontaneous remission without recurrence.

Any acute case which persists or relapses after remission should be considered with the group of chronic thrombocytopenias. In this group splenectomy is the treatment of choice, and produces a complete cure in 60–70% of cases.

Cortisone or A.C.T.H. may be used to prepare cases for operation or to treat those refusing operation. These drugs may be the treatment of choice in mildly affected cases and those failing to respond to splenectomy. In a very few cases they have unpredictably promoted permanent remission.

Recent research into immuno-purpura has proved the existence of anti-platelet antibodies in certain forms of essential thrombocytopenia. At present, however, these observations have not established any new therapeutic criteria. They have, however, explained why fresh platelet transfusions so often fail to have any haemostatic effect in cases of thrombocytopenic purpura.

Heredity in Schilder's Disease

Q.—*What is the prognosis for future children of a young married couple whose first child died of Schilder's disease? There is no family history of neurological disease on either side. Has this condition any association with Rhesus incompatibility, as the father is Rh positive and the mother Rh negative?*

A.—The term Schilder's disease (encephalitis periaxialis diffusa) probably includes several diseases of different aetiology. In a proportion of instances the condition is due to a recessive gene, and then the risk to a further child is 1 in 4; but since it is not known what proportion of all cases are caused in this way, the parents should be told that there is an increased risk of another child being affected, but the risk is not precisely known. If on inquiry it is found that the marriage is consanguineous, then the probability that a recessive gene is concerned is much increased. If the child dies, it would be helpful to have an expert opinion on whether the histological appearance of the brain does or does not resemble that seen in the reported cases where more than one child in a family has been affected. The condition has no association with Rhesus incompatibility.

Smog and Tuberculosis

Q.—*Is there any evidence that smog has an adverse effect on quiescent pulmonary tuberculosis?*

A.—There is no evidence that smog has any direct effect on tuberculous changes in the lungs. A patient with a localized, well-healed, tuberculous lesion, uncomplicated by secondary changes in the bronchi, should not suffer any special ill-effects. Patients who have had extensive pulmonary tuberculosis will inevitably be left with a certain amount of pulmonary fibrosis after healing of the tuberculosis, and this condition is often complicated by chronic bronchitis and possibly by localized dilatation of the bronchi in the more severely affected parts. Such patients would, of course, be liable to exacerbations from smog like any other chronic bronchitics. An exacerbation of bronchitis of this sort may be complicated by a simple bronchopneumonia, and it would be difficult to deny the possibility that this might cause activation of quiescent tuberculosis.

Intrauterine Contraceptive Devices

Q.—*What is the present view of intrauterine contraceptives? How safe and reliable are they? Is special skill required to fit them?*

A.—Few persons in medical practice in this country have much experience of intrauterine contraceptives. Their views are necessarily influenced by the fact that such experience is attained when they are called upon to rescue patients from the extremely serious consequences which can occur as a result of the use of such contraceptives. It is impossible to say how common these serious consequences may be, but the mere fact that peritonitis and pelvic cellulitis can occur makes it desirable to adopt some other form of contraceptive device. This advice is reinforced from the knowledge that the intrauterine devices are by no means completely reliable. From time to time in films which have been taken in advanced pregnancy radiologists have observed the presence in the tissues of metallic contraceptives.

Operative Treatment of Deafness in Children

Q.—*Is operative treatment ever worth considering in cases of deafness in young children? If the answer is yes, what are the criteria for operation, broadly what is done, and what improvement may be expected?*

A.—Deafness in young children is due in the majority of cases to degenerative and inflammatory processes affecting the inner ear and resulting in a perceptive type of hearing loss. In such cases no surgical treatment is of any value at all. There are, on the other hand, conditions causing a conductive type of deafness in which surgery may well play a useful role. The following two conditions deserve mention:

(1) *Atresia Auris Congenita*: In this condition a complete or partial absence of the auricle is present which may be bilateral. Radiographs of the petrous bones will show the presence or absence of the middle or internal ear. If these are present, operation is worth consideration. Ruedi[1] has recently reported his results after operation on 19 ears. Although the indications to operate and the technique to be used are still not quite settled, the prospects of success are now quite favourable in these cases.

(2) *Juvenile Otosclerosis*: This type of inherited deafness is not congenital, that is to say, present at birth, but commonly becomes manifest during the school years. It is

characterized by a strong familial tendency and causes deafness by fixation of the stapes through its involvement in a pathological process affecting the bone of the labyrinthine capsule. Lempert, of New York, and others in this country have been able to restore the hearing by means of the fenestration operation. A window is made by removal of bone over the horizontal canal, thus providing an alternative pathway for sound to the cochlea. Otosclerosis is more likely to be in a progressive stage in children than in adults, as evidenced by increasing deafness and sometimes a flamingo-pink tint of the tympanic membranes. Operation is not advisable in this stage of the disease. Excellent results have been obtained by fenestration in suitable cases of otosclerosis, and the opinion of an aural surgeon should most definitely be sought in such cases.

REFERENCE

[1] *Laryngoscope*, 1954, **64**, 666.

The Hookah and Lung Cancer

Q.—*Does the custom of filtering tobacco smoke through water as in the Eastern hookah remove the noxious elements? Carcinoma of the lung is very rare, in my experience, in hookah-smoking Indians.*

A.—In order to answer this question analyses of tobacco smoke before and after passage through water would be required, and so far as I know this has not been done. Such treatment would remove chiefly water-soluble constituents, but these might carry other compounds with them. Very probably there are carcinogenic compounds in tobacco smoke which we do not know, and hence their presence or absence could not be determined. Such filtration processes usually do not remove any one compound completely and their action is therefore only equivalent to smoking less tobacco. One can feel pretty sure that if the removal of constituents was very drastic the smoke would cease to have much attraction for the smoker and hence he would cease to use the hookah. Any data about the incidence of cancer of the lung in hookah-smokers would be very welcome.

Pituitary Extract in Cretinism

Q.—*Is pituitary extract of any value in the treatment of cretinism? If so, please state recommended dosage and mode and duration of administration.*

A.—Pituitary extract (thyrotrophic fraction) acts by stimulating the thyroid gland to secrete an increased amount of thyroid hormone. In sporadic cretinism the thyroid gland is absent or there are only fragments of thyroid tissue, and in endemic cretinism the gland is atrophic and fibrosed and cannot respond to stimulation. Pituitary extract is thus of no value in the treatment of cretinism. A further disadvantage of pituitary extract is that after it has been administered for a few weeks refractoriness develops as a result of the formation of an antihormone factor.

Aetiology and Treatment of Intermenstrual Pain

Q.—*What is considered the cause of intermenstrual pain (mittelschmerz)? How should a severe case be managed?*

A.—Cyclic intermenstrual pain was probably first described in 1847 by Pouchet, who attributed it to tubal contractions propelling the ovum towards the uterus. The exact cause is not yet known, but both the pain and the commonly associated vaginal spotting of blood are said to be due to a temporary drop in oestrogen level at the time of ovulation, combined with an as yet inadequate secretion of progesterone. With further development of the corpus luteum, the production of these hormones rises and the symptoms abate within a day or two. The correlation of the pain with the time of ovulation can be demonstrated by its coincidence with the temperature shift in the basal body temperature chart.

Two types of pain are described. The first, sharp in character and limited to one or other iliac fossa, recurs over one or two days; it is thought to be due to the irruption into the peritoneal cavity at ovulation of either follicular fluid or blood from a ruptured vessel overlying the mature follicle. Wharton and Henriksen[1] studied 61 cases of mittelschmerz, but in less than half of those subjected to surgery was free blood found in the peritoneal cavity. The second type of pain, intermittent and cramping, is sited in the hypogastrium, and is presumed to be due to uterine contractions. This variety is more likely to be accompanied by vaginal spotting.

With the cause uncertain, many forms of treatment have been essayed. In all cases the woman should be assured that the pain is not due to disease, but is in a way evidence of normal ovarian function. As such it may be treated simply with analgesics. In the more severe cases ovulation may be suppressed with oestrogens or androgens, but this is "unphysiological," while radiotherapy, which has also been advocated, is rather drastic. Probably the most rational therapy is to give either small doses of oestrogens (0.5 mg. stilboestrol) or larger doses of progestogens (30 mg. ethisterone) daily by mouth, commencing three days before the pain is expected, and continuing for five or six days. If this fails, small doses of oral androgen (10 mg. methyl testosterone) may be given daily throughout the intermenstruum, as suggested by Greenblatt.[2] Whichever form of hormone therapy is used, it can be discontinued after three or four cycles with a good prospect of non-recurrence of the pain, for there is in any case a tendency to spontaneous cure.

REFERENCES

[1] Wharton, L. R., and Henriksen, E., *J. Amer. med. Ass.*, 1936, **107**, 1425
[2] Greenblatt, R. B., *Amer. J. Obstet. Gynec.*, 1943, **45**, 299.

NOTES AND COMMENTS

Shou'd Oral Diuretics be Tried First?—Dr. G. R. Fryers (Medical Director, John Wyeth and Co. Ltd., London, N.W.1) writes: Your reply to a query on the use of oral diuretics (September 24, p. 802) advises intramuscular diuretics in serious cases of heart failure. This answer overlooks the advantages of the equally effective and reliable organic mercurial mercaptomerin sodium ("thiomerin"), which has much less toxicity, is given by subcutaneous injection, and can therefore usually be given into a non-oedematous area, with consequent predictability of absorption.

Our Expert writes: The undesirable effects of mercurial diuretics include sudden death from cardiac arrest, delayed sensitization to mercury, mercurial poisoning resembling the toxic effects of inorganic mercury compounds, and disturbances of body fluid arising in consequence of the diuretic effect. Subcutaneous preparations share with intramuscular preparations the immunity from causing sudden cardiac arrest observed only after intravenous mercurials. All the other types of undesirable effects have been observed after subcutaneous mercurials, and it is doubtful whether they are less frequent with subcutaneous mercurials, having regard to the infrequent use of these as compared to intramuscular mercurials. Patients who have become sensitized to intramuscular mercurials may tolerate subcutaneous mercurials for a time, later becoming sensitized to these also.

Corrections.—In the paper by Professor Wilfrid Gaisford and Dr. R. F. Jennison[1] (September 17, p. 700) there was an error at the foot of Table III: the difference of means at 16 weeks was 12.6% (not 22.6%).

In the article entitled "Treatment of Chronic Lead-poisoning with Calcium Disodium Versenate" by Drs. A. C. Markus and A. G. Spencer and in the leading article on "Lead Poisoning in Children" (October 8, pp. 883 and 894), we regret that it was not made clear that "versenate" is a proprietary name.

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